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CONTENTS OF VOL. CLXX

ORIGINAL ARTICLES

The Prevention of Simple Goiter. By J. C. HATHAWAY, M.B. . . .	1
Purpura Hemorrhagica (Thrombocytopenic Purpura) with Report of a case with Splenectomy. By DAVID L. FARLEY, M.D. . . .	10
Wassermann-fast Syphilitics Treated with Bismuth. By LAWRENCE K. McCAFFERTY, M.D., and J. ARNOT MACGREGOR, M.D. . . .	22
The Wassermann Reaction in the Blood and Spinal Fluid of Paretic Neurosyphilis, with the Presentation of the Results in One Hundred and Sixty-six Consecutive Hospitalized Cases. By WILLIAM C. MENNINGER, M.D., and KARL A. MENNINGER, M.D. . . .	27
Conditions Simulating Acute Lymphatic Leukemia (Infectious Mononucleosis. Tuberculosis). By JOHN FITCH LANDON, M.D. . . .	37
Differentiation of Amebic Dysentery from So-called Idiopathic Ulcerative Colitis. By LAURENCE H. MAYERS, M.D., and EDWIN F. HIRSCH, M.D. . . .	43
Duodenal Diverticulosis, with Report of a Case Seen Roentgenologically. By EMANUEL W. LIPSCHUTZ, M.D. . . .	53
Three Cases of Tularemia, One Resembling Sporotrichosis. By F. CHURCHILL HODGES, M.D. . . .	57
Malignant Tumors of the Thyroid: An Analysis of Seven Cases with a Study of the Structure and Function of the Metastases. By DAVID EISEN, M.B. (Tor.) . . .	61
The Kottman Reaction in Thyroid Disfunction. By DAVID W. KRAMER, M.D. . . .	75
Further Studies of Cerebrospinal Fluid in Infants and Young Children. By STAFFORD McLEAN, M.D., and FREDERICK H. VON HOFE, M.D. . . .	82
Early Bed-sores as a Diagnostic Sign of Carbon Monoxid Poisoning. By MEYER A. RABINOWITZ, M.D. . . .	98
Primary Carcinoma of the Lung. By HENRY MONROE MOSES, A.M., M.D., F.A.C.P. . . .	102

Blood Transfusion: Its Dangers and Limited Value. By J. F. BALDWIN, M.D., F.A.C.S.	118
A Consideration of the Clinical Value of Ephedrin, with a Report on Its Effects in Certain Special Cases. By T. GRIER MILLER, M.D. . . .	157
One Hundred Consecutive Cholecystectomies. By WILLIAM O. JOHNSON, M.D.	181
A Review of Twenty-eight Cases of Purpura Hemorrhagica in which Splenectomy was Performed. By HERBERT Z. GIFFIN, M.D., and JACKSON K. HOLLOWAY, M.D.	186
A Clinical Study of Quinidin Therapy. By HERMAN H. RIECKER, M.D. . . .	205
Experimental Gastric and Duodenal Inflammation and Ulcer. By ALBERT HOFFMANN	212
The Sigmoidoscopic Picture of Chronic Ulcerative Colitis (Non-specific). By BURRILL B. CROHN, M.D., and HERMAN ROSENBERG, M.D. . . .	220
The Possible Relationship Between Guanidin and High Blood Pressure. By RALPH H. MAJOR, M.D.	228
Calorimetric Studies of the Extremities following Lumbar Sympathetic Ramisection and Ganglionectomy. By GEORGE E. BROWN, M.D., and ALFRED W. ADSON, M.D.	232
Disease of the Coronary Arteries. By M. H. NATHANSON	240
Rectal Ether Analgesia in Childbirth. By JAMES A. HARRAR, M.D. . . .	256
A Report of an Interesting Type of Diaphragmatic Hernia of the Cardia of the Stomach Through the Esophageal Orifice. By JULIUS FRIEDENWALD, M.D., and MAURICE FELDMAN, M.D.	263
Iodin Hyperthyroidism. By ARNOLD S. JACKSON, M.D.	271
Adiposity and Other Etiologic Factors in Diabetes Mellitus. By JAMES M. ANDERS, M.D., and H. LEON JAMESON, M.D.	313
Problems in the Diagnosis and Treatment of Infiltrating Tumors of the Cerebral Hemispheres, with Remarks on a New Surgical Procedure. By CHARLES A. ELSBERG, M.D.	324
Leptospirosis Icterohemorrhagica (Weil's Disease). By JOSEPH SAILER, M.D.	332
A Tintometer for the Analysis of the Color of the Skin. By LEONARD G. ROWNTREE, M.D., and GEORGE E. BROWN, M.D.	341
Giardiasis: Its Frequency, Recognition, Treatment and Certain Clinical Factors. By B. B. VINCENT LYON, A.B., M.D., and WILLIAM A. SWALM, M.D.	348

Tropical Sprue in a Child Six Years of Age: With Isolation of Monilia from Patient and Tissues of Inoculated Animal. By GERTRUDE JOHNSON, M.D., and F. T. BREIDIGAIN, B.S.	364
Severe Anemias of Pregnancy and the Puerperium. By RALPH C. LARRABEE, M.D.	371
Nonfatal Carbon Monoxid Poisoning. Report of a Case. By BERNARD J. ALPERS, M.D.	390
The Effect of Spleen Extract and Bone Marrow on the Blood Picture in Pulmonary Tuberculosis. By ROYAL W. DUNHAM, M.D.	394
Report of Six Cases of Pyelitis in the Newly-born Infant. By R. H. GRAHAM, M.D.	401
The Practical Value of Neutral Red as a Test for Gastric Secretory Function. By GEORGE MORRIS PIERSOL, M.D., H. L. BOCKUS, M.D., and J. BANK, M.D.	405
Unusual Eosinophilia with Splenomegaly (Eosinophilic Leukemia?) in a Child Aged Six Years. By MURRAY H. BASS, M.D.	416
Increased Permeability of Vessel Walls as a Frequent Cause of Pulmonary Hemorrhage. By F. M. POTTENGER, M.D.	420
Observations on Nonpostcicatricial Keloid. With a Report of a Case. By GEORGE L. WALDBOTT, M.D.	425
Subphrenic Abscess: A Clinical Study. By LOUIS TUFT, M.D.	431
The Relationship of the Sympathetic Innervation to the Tone of Skeletal Muscle. By the late JOHN I. HUNTER, M.D., CH.M.	469
Some Notes on Cancer. II. On Human Intestinal Parasites as a Cancer Inciting Factor and on the Significance of the Precancerous State. By WILLY MEYER, M.D.	481
Carcinoma of the Esophagus with Especial Reference to Site. By WILLIAM CHARLES BUCHBINDER, M.D.	496
A Form of Acute Hemolytic Anemia Probably of Infectious Origin. By MAX LEDERER, M.D.	500
Clinical Value of Some Recent Tests for Liver Function. By HOWARD F. SHATTUCK, M.D., JOHN C. BROWNE, M.D., and MAJORIE PRESTON, A.B.	510
Further Clinical and Operative Studies of the Icterus Index. By JOHN V. BARROW, M.D., EUGENE L. ARMSTRONG, M.D., and WILLIAM H. OLDS, M.D.	519

Mitral Stenosis after the Fifth Decade of Life. By ERNST P. BOAS, M.D., and DAVID PERLA, M.D.	529
Atypical Tabes Dorsalis (Forme Fruste): Surgical Errors in, with Leading Points in Diagnosis. By A. E. BENNETT, M.D.	538
Glucose Tolerance Tests in Children. I. Based on Body Weight. II. Based on Nutritional Surface and Body Surface. By MARGARET E. FRIES, M.D., and JEROME L. KOHN, M.D.	547
Comments on Body Weight in Relation to Health and Disease. By ERNEST S. DU BRAY, M.D.	564
Physical Defects as Revealed by Periodic Health Examinations. By LOUIS I. DUBLIN, EUGENE LYMAN FISK, and EDWIN W. KOPF . . .	576
The Biliary Aspects of Liver Disease. By PEYTON ROUS, M.D. . . .	625
Rheumatic Fever. By HOMER F. SWIFT, M.D.	631
Clinical Observations on the Value of Calcium Chlorid as a Diuretic and Its Influence Upon the Circulatory Mechanism. By HAROLD N. SEGALL, M.D., and PAUL D. WHITE, M.D.	647
The Value of Venesection in the Treatment of the Decompensated Heart. By BURGESS GORDON, M.D.	671
Microcytosis in Hemolytic Icterus. By B. R. WHITCHER, A.B., M.D. . .	678
The Magnesium and Calcium Content of the Blood and Blood Plasma of Tuberculous Patients. By EDWARD W. SCHOENHEIT, M.D. . . .	689
The Nontuberculous Pulmonary Fibroses. By DOROTHY W. ATKINSON, M.D.	693
A Study of Four Hundred and Fifty Cases of Epidemic Encephalitis. By JOSEPHINE B. NEAL, M.D., HENRY W. JACKSON, M.D., and EMANUEL APPELBAUM, M.D.	708
The Role of Focal Infections in the Etiology of Eczema. By JOHN W. VISHER, M.A., M.D.	723
A Study of the Effect Produced on the Enzyme Concentration of the Duo- denum by the Oral Administration of Certain Commerical Pancreatic Preparations. By DANIEL N. SILVERMAN, M.D., W. DENIS, Ph.D., and STELLA LECHE, M.Sc.	727
Simple Lactating Adenoma of the Breast. By ALBERT E. BOTHE, M.D. .	731
The Pharmacologic and Therapeutic Properties of the Sulphocyanates. By JOHN BENJAMIN NICHOLS, M.D.	735

Abdominal Pain Due to Epigastric Hernia. By J. WILLIAM HINTON, M.D.	748
The Nature and Mode of Regulation of Glomerular Function. By A. N. RICHARDS, PH. D.	781
Studies in Human Constitution. III. Physical Types in Relation to the Toxemias of Pregnancy. By GEORGE DRAPER, M.D.	803
Observations on the Diagnosis of Subphrenic Abscess. By RICHARD DEXTER, M.D.	810
Generalized Tuberculous Adenitis with Report of a Case. By LEO H. CRIEP, M.D., and FRED C. NARR, M.D.	822
Spontaneous Rupture of the Heart. A Clinicopathologic Study Based on 22 Unpublished Cases and 632 from the Literature. By E. B. KRUMBHAAR, M.D., PH.D., and C. CROWELL, A.B., B.S.	828
Relation of Morphology to the Prognosis of Aortic Syphilis. By W. W. G. MACLACHLAN, M.D.	856
The Neurological Mechanism of Angina Pectoris and Its Relation to Surgical Therapy. By WILDER PENFIELD, M.D.	864
Lipiodol in Neurosurgery. With a Report of a Case with Deleterious Results. By A. S. MACLAIRE, M.D.	874
Acute Typhoid Cholecystitis Forty-one Years after Original Infection. By LAWRENCE A. POMEROY, M.D., and JAMES K. SHEN, M.D.	881
The Effect of Roentgenotherapy on the Human Heart. By E. S. EMERY, JR., M.D., and BURGESS GORDON, M.D.	884
A Quantitative Determination of Intestinal Putrefaction. By N. JEAN NOVELLO, M.A., WILLIAM WOLF, ScD., M.D., and C. P. SHERWIN, Sc.D., M.D.	888
(Left) Shoulder Pain of Phrenic Origin—A Reflex Symptom in Chronic Appendicitis; with a Report of Three Cases. By IRVING GRAY, M.D.	894

REVIEWS

Reviews of Books	127, 284, 442, 595, 753, 900
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PROGRESS OF MEDICAL SCIENCE

Medicine	133, 289, 447, 599, 757, 905
Surgery	137, 290, 449, 601, 759, 907
Therapeutics	606, 910
Pediatrics	140, 293, 453, 609, 763, 912
Dermatology and Syphilis	143, 613
Gynecology	145, 296, 457, 615, 766, 914
Neurology and Psychiatry	303, 769, 921
Oto-Rhino-Laryngology	299, 462, 618, 772, 917
Radiology	148, 302, 919
Pathology and Bacteriology	151, 304, 463, 622, 775
Hygiene and Public Health	154, 308, 467, 778, 922
Physiology	924



I. MINIS HAYS, A.B., A.M., M.D.

II. MINIS HAYS, A.B., A.M., M.D.

WITH the death of DR. I. MINIS HAYS on June 5 there passed a man whose name was connected with THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES for over half a century.

Dr. Hays was born in Philadelphia on July 26, 1847, the son of Dr. Isaac Hays, himself for many years a prominent figure in Philadelphia medicine, and Editor of this JOURNAL from 1833 to 1877. He was graduated from the University of Pennsylvania, receiving the degrees of A.B. (1866), M.D. (1868) and A.M. (1869). In the latter year he became Assistant Editor of the AMERICAN JOURNAL OF THE MEDICAL SCIENCES, eventually succeeding his father to the editorship in 1878, a position which he held until 1890. He also edited the *Medical News* from 1878 to 1889. He wrote a number of articles in the domain of his specialty, ophthalmology, and edited the American edition of J. Soelberg Wells' *Treatise on the Diseases of the Eye*, which appeared in 1873.

As a member of the Association of American Physicians and of the College of Physicians of Philadelphia, he took an active part in the councils of his profession, and the College is indebted to him for twenty years of fruitful service as Chairman and Member of the Library Committee. In 1876 he was Secretary-General of the International Medical Congress which met in Philadelphia at the time of the Centennial.

But his interests extended beyond the sphere of medical activities, and it is as Secretary of the American Philosophical Society in the last twenty-eight years of his life that he will be especially remembered. For the space of a generation his was the guiding hand in the success of that organization. Particularly interested in its founder, Benjamin Franklin, he published a "Chronology of Benjamin Franklin" in 1904, of which a second edition appeared in 1913, and a "Calendar of the Franklin Papers" in 1907. The successful celebration in Philadelphia of the Franklin Bi-centenary in 1906 was largely due to Dr. Hays' efforts. Our knowledge of Franklin as a personality owes much to the historical researches of Dr. Hays.

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES takes this opportunity to pay tribute to his memory.

THE
AMERICAN JOURNAL
OF THE MEDICAL SCIENCES

JULY, 1925

ORIGINAL ARTICLES.

THE PREVENTION OF SIMPLE GOITER.

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(From the Laboratory of Physiological Chemistry, University of Minnesota.)

SIMPLE, or endemic, goiter is one of the oldest maladies known to the world today. Mention of this occurrence may be found in the earliest medical literature. Extensive forms of exorcisms for goiter may be found in the Arthorva Veda, ancient Hindoo collection of writings, dated about 2000 B. C. A review of historical literature shows numerous publications on this subject at intervals up to the present time. It has been known in nearly all lands, and the sum total of its ravages throughout the ages has been enormous, yet it is only within recent years that methods for its prevention have been instituted. People living in maritime districts have had no cause to be concerned, while those living in inland districts have grown accustomed to regard it as a natural or normal state.

As statistics from various localities have revealed the existence of goiter from year to year, the truly astounding incidence of this disease has become manifest. In many of the goitrous districts more than half the people have large visible goiters. Goiter surveys showing the high incidence have been recognized as being essential in order to institute preventive measures, and are being conducted or are under contemplation in many places at the present time. Observation and surveys show that it is most prevalent during childhood, adolescence and during the period of pregnancy. Girls are affected about two to three times as frequently as boys.

The great geographical regions of endemic goiter, as is well known, are the Alpine regions of Switzerland, Italy, France, southern Germany and southern Austria; the Himalayan districts of India, southwestern China and eastern Mongolia; the Andes region of South America; the Great Lakes Basin, and the Cascade Mountain regions of Oregon, Washington and British Columbia, in this continent. A great many regions are known which may be classed as mildly and moderately goitrous. Nearly every country in the world has some districts which may fall into one of the latter classes.

Recently the situation has come more and more into the public eye. Papers on various phases of goiter are common in scientific and pseudoscientific literature and are not infrequent in the periodicals and newspapers of the day. The time is now ripe for the institution of extensive preventive measures in all the involved areas.

Incidence While simple goiter may develop sporadically in almost any locality, as it did during one of Captain Cook's voyages, its strongholds have been in plateaus and mountain districts as in contradistinction to seacoast countries. Hirsch, in his publication on "The Historical and Geographical Relations of Goiter," in 1860, outlined these areas. As early as 1874 Baillarger, of the French Commission, estimated that there were 500,000 cases in France alone. A little later Kocher's statistics showed that 80 per cent of the school children of Berne were goitrous. Recently, in 1918, the health commissioner of the Canton of St. Gall showed the goiter incidence among school children to be 87.6 per cent. Klinger¹⁷ states that 100 per cent of the school children are goitrous in some of the schools of Zürich, where he is carrying out methods of goiter prevention.

Schittenhelm and Weichardt³¹ estimate the incidence of goiter in southern Bavaria as being 77 to 89 per cent of the total population. In Italy, from 1859 to 1864, 3 per cent of conscripts were excused from service because of this affliction. In Switzerland 12,207 men were exempted from military duty for this cause from 1875 to 1881. In 1912 McCarrison²⁰ reported 4869 cases in the district of Monghyr and 3142 cases in Bhagalpur in India, both of which districts lie in the Himalayan Mountains. He estimated that 20 per cent of the people in the Gilgit district (population, 70,000) had goiter. In the goitrous regions of Europe the percentage is even higher, as is shown above. In the United States a great many surveys have been recently made and statistics come pouring in. The following examples, which are all very recent, give an insight into the situation in all of the great goitrous regions of this country. Kerr¹³ reported the examination of 21,182 recruits at Camp Lewis, Washington, and found 21 per cent having large and well-developed goiters. Smith³⁴ reports the examination of 65,507 men represent-

ing fifteen different central and western states at Jefferson Barracks, Missouri, with an incidence of 1.63 per cent showing large goiters. Hall⁹ found 18 per cent enlargements in 2086 men (average age twenty years, five months) and 31 per cent of 1253 women (average age nineteen years, three months) at the University of Washington. Levin¹⁸ examined 1783 unselected persons in two townships in the Great Lakes goiter belt (Houghton County, Mich.) and found 1146 goiters. Olsen and Clark²⁶ found 58 per cent of 4061 school children in thirteen localities in Minnesota to have goiters. In Montana²⁸ 13,937 school children were examined and 22 per cent found to have goiter. Olin²⁷ reports 47 per cent in 31,612 school children examined in Michigan. Marine and Kimball²⁵ examined nearly 10,000 school girls in Akron, Ohio, and found 56 per cent to have goiters. A recent survey in St. Paul,³⁰ Minn., showed 60 per cent thyroid enlargements in 582 high school pupils and 4615 grade school children examined. Clark⁵ examined 13,836 school children in eleven counties of West Virginia and found about 9 per cent incidence; 6432 children in nine Virginia counties showed 12.7 per cent according to the same writer.

All of these statistics merely give an indication of the enormous degree of prevalence of this disease. Detailed surveys are now in progress in many of the goitrous regions, an instance of which is Utah, where Wallace is just completing the examination of over 100,000 children. This information is of the greatest value, as it is the basis for all successful measures of goiter prevention.

Etiology. Simple goiter has been associated with water as the etiological factor as far back as the history of goiter goes. According to Barton,¹ the American Indians were convinced of this relation. The natives of central Africa made this association (Livingston) as also did Hippocrates in his writings. The history of goiter is marked with numerous theories as to the causative factor; however, no one at the present time who has studied the situation considers goiter an idiopathic enlargement of the thyroid. A great many men have worked upon this problem during the last century, and a definite cause has been found for the immediate, if not for the remote, factor causing endemic goiter.

McCarrison²⁰ has done a large amount of work in an endeavor to find the causative factor, and believes it to be due to a water-borne infection, possibly a bacterium of the colon group. A few other workers, notably Shepherd³² in his 1918 report on the occurrence of goiter in Canada, inclines to this view. However, in his more recent articles, McCarrison²⁰ attempts to reconcile his view with those who consider goiter a deficiency disease.

It has been said that the chemical constituents and also the bacterial content of drinking water in any locality are largely influenced by the nature of the soil and underlying rock strata. Goiter is more prevalent in the regions underlaid by the Silurian,

Carboniferous and Permian systems; while those of eruptive or crystalline rocks of the Archean groups, the sediment of Jurassic, Cretaceous and post-Tertiary seas, as well as fresh water deposits, are comparatively free from affection. Just how much influence this has upon the etiology of goiter is difficult to state.

Iodin starvation is now considered to be the immediate cause of simple goiter. Chatin,⁴ a French chemist, first demonstrated this about 1850. He analyzed the water, food, air and soil of goitrous and nongoitrous regions, finding the goitrous areas to be low in iodine and the nongoitrous high. He advanced the hypothesis that goiter was due to a deficiency of iodine. The Commission appointed by the Paris Academy of Science to examine Chatin's work supported his analyses, but would not accept his conclusions concerning goiter, as it was impossible for them to attribute any virtue to $\frac{1}{400}$ mg. of any substance. However, his conclusions in general are accepted today.

Since Chatin's work several investigators have corroborated the facts by extensive analyses. Recently von Fellenberg,³⁶ and his collaborators in Switzerland, and McClendon and Hathaway²³ in this country, using more accurate methods and making many determinations, have demonstrated beyond a doubt that simple goiter is due to an insufficient quantity of iodine in food and drinking water. They have shown that food from nongoitrous regions may contain from 100 to 200 per cent more iodine than the same food from goitrous regions and that nongoitrous waters may contain as much as 20,000 times as much iodine as goitrous waters. They have also demonstrated experimentally the approximate amount of iodine that must be consumed daily to prevent the occurrence of goiter. The results of both of these groups of investigators are about the same and both come to about the same conclusions. Olin²⁷ and his collaborators, in making detailed surveys of the Michigan water supplies, are of the same opinion.

Baumann,² in 1896, demonstrated that the active principle of the thyroid contained iodine and indicated its relation to metabolism. In 1916 Kendall¹² definitely determined this substance as tri-iodo-indol-propionic acid and showed that it contained about 65 per cent iodine. He also demonstrated by animal experimentation its physiological action, and that its physiological action is proportional to its iodine content. Further animal experimentation, largely by Marine and Lenhart,²⁴ has shown that any substance substituted for iodine, destroys the physiological action of thyroxine, the thyroid hormone. It has also been proved histologically that glandular hypoplasia of the thyroid is due to a deficiency of iodine, and that if the content is maintained at or above 0.1 per cent no anatomical changes occur.

The most excellent work of Marine and Kimball²⁵ in this country, and the researches of Hunziker,^{10, 11} Eggenberger⁷ and more recently

Klinger,¹⁷ in Switzerland, have shown absolutely that iodine in small quantities will prevent, and in larger quantities cure, simple goiter. Their striking results will be reviewed later in discussing methods of prevention.

What further evidence is necessary to establish the fact that this disease is due to iodine starvation?

Methods of Prevention. Iodine preparations have been unwittingly used as a goiter cure for centuries. Burnt sponge was used as a treatment by the Chinese over four thousand years ago and is also reported to have been used by the ancient Greeks. Dumas and Coindet,⁶ in 1820, used iodine in the treatment of goiter, and from that time until about 1896 it was practically the only treatment used. Since Baumann's work in 1896, and the research of other men since that time, knowledge concerning the chemistry of the thyroid has become much better known and more definite methods of treatment have been instituted.

Up to the year 1917 no preventive measures of any extent had been instituted anywhere. Several physicians in private practice had advocated measures before this time, but the credit for the beginning of practical application of preventive methods to a large extent goes almost entirely to Marine and Kimball.^{14, 15, 16} Marine and Lenhart²⁴ laid the foundation for this when they produced definite and convincing evidence that thyroid hyperplasia (goiter) could be prevented in animals by the administration of small amounts of iodine as sodium iodide.

(1) Marine and Kimball²⁵ gave prophylactic iodine to about 10,000 girls for at least one school term, these observations extending over a period of four years. They watched about 4000 for a period of from two to four years, during which time approximately one-half took enough iodine to saturate the thyroid twice a year, in the spring and fall. The other half took no iodine. They state that "Among those who took iodine as directed, who were normal when the administration was started, not one developed goiter, while among those who did not take iodine 27.6 per cent developed goiter. Moreover, among those who had goiters and took iodine systematically, in more than 60 per cent the thyroid gland returned to normal size; while among those who did not take iodine, in comparatively very few did the thyroid gland show any tendency to decrease in size." They first used 2 gm. of sodium iodide over a period of two weeks and repeated this dose twice yearly. They have changed their methods from time to time, and now advocate giving 10 mg. weekly throughout the school year in the form of chocolate-coated tablets of iodine in organic form.

Klinger¹⁷ reports similar but even more striking results in three cantons of Switzerland. Muggio, using the same method throughout the districts of Sondrio, Italy, has had extremely good results. Contrary to medical opinion, these researches reveal the startling

cities on the western coast contains thirty times as much iodine as has been advocated for prophylaxis, and the possibility of their water being "poisoned" has never been contemplated by those living in these cities.

4. Some men feel that the treatment of the individual would be better. If the physicians of the country and the laity could all be educated as to the necessity of prophylactic iodine, this would undoubtedly be the better, although vastly more expensive, course to follow. However, such education would be a large problem, requiring many years to fulfil, and at the best the results would be uncertain. Furthermore, it would necessitate a large amount of work on the part of the public health officials in making sure that proper iodine prophylaxis was used in all places where it was a necessity, and such a procedure would entail enormous expense.

5. Some medical men have voiced the opinion that such a measure would have a deleterious effect on exophthalmic goiter. The results at Rochester, N. Y., do not show any evidence of this. The use of other methods of prophylaxis both here and abroad, where much larger doses have been in vogue, shows that not in a single instance has this occurred. Moreover, Plummer, at the Mayo Clinic, who probably has the largest series of exophthalmic goiter cases on record, has been using iodine in the treatment of these cases for some time, and reports excellent results.

6. It has been contended that the addition of iodine to the water supply is wasteful, and therefore expensive. It is probably true that less than 1 per cent of the water in a city is used for drinking purposes. Since this is true, why pay large sums yearly in purifying water for drinking purposes, over 99 per cent of which is wasted? Yet, that is what we do. In the one case the removal of pathogenic bacteria prevents water-borne disease, while in the other, the addition of the iodide prevents goiter. Is it not just as imperative that we spend small amounts to prevent one disease as to spend much larger amounts to prevent others?

The addition of sodium iodide is really inexpensive. The city of Rochester, N. Y., with a population of about 315,000, spends \$3000 per year, or less than 1 cent a year per person. This certainly is not so expensive a procedure but that we can afford to waste a certain amount. Moreover, some of the iodine wasted is used in watering stock and irrigating food plants and is thus returned to the human system.

It has been claimed that the use of iodine in tablet form is the most economical. Whereas sodium iodide in the water supply costs about 1 cent per year per person, druggists sell these tablets at the rate of about \$1.50 per year per person, although a special wholesale rate at the small price of about 50 cents per year per person may be made to schools. We can afford to waste a little iodide from our water supplies and thereby save considerable money.

7. The economists have brought forth the theory that wholesale treating of water supplies would soon deplete the world's source of iodine. The world's supply of iodine is so huge that we cannot conceive of it. McClendon has calculated that the sea contains about 66,000,000,000 tons. This iodine is extracted at a rapid rate by sea weed and industries could easily be developed to utilize it.

Conclusions. *Eradication of Goiter.* A method which would control the goiter situation should consist of the following:

1. Detailed surveys should be made of all localities where goiter is suspected. This is the basis for all successful methods of goiter prevention.

2. The institution of treatment with sodium iodide of the water supplies of all cities and towns which prove to be goitrous.

3. Small villages not having a common water supply, and rural communities, must have iodine supplied either by the use of iodized table salt or by iodine tablets of some kind.

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PURPURA HEMORRHAGICA (THROMBOCYTOPENIC PURPURA) WITH REPORT OF A CASE WITH SPLENECTOMY.

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SIR WILLIAM OSLER¹ referred to purpura as "That obscure and interesting manifestation of which we know so much and at the

same time so little." Since Osler made this reference much has been done to properly classify conditions accompanied by purpura. The present-day conception of the classification and diagnosis of primary purpuric disease still resembles, however, the state of the conception a number of generations ago of intermittent fever. Knowing the exact etiology of malaria as we now do, we can project the probable fact that patients suffering from intermittent fever of pyogenic origin were grouped together with patients infested with the plasmodium of malaria and considered as having an identical disease. Atypical cases of malaria without intermittent fever no doubt escaped true classification.

Aplastic anemia, purpura hemorrhagica, and acute myelogenous leukemia may show clinical signs and symptoms of very similar character—an acute downward fatal course, hemorrhages from mucous membranes, purpuric eruption, reduction of blood platelets, prolonged bleeding time and profound anemia. In the majority of cases final classification into one of the three groups is possible. But borderline cases occur where the exact diagnosis must remain in doubt, even in the presence of collected evidence from history, physical examination, clinical laboratory data, and postmortem examination of tissues. No one at the present time is able to say, definitely, whether these three diseases are or are not related. E. Frank, the distinguished German hematologist, believed primary aplastic anemia and purpura hemorrhagica to be the same disease. Others equally distinguished are of a different opinion.

In the year 1731, Werlhof² separated purpura hemorrhagica from the general group of purpuric diseases. Hayem³ in 1889 emphasized the observation, published by Denys⁴ two years previously, that the blood platelets were present in markedly decreased number in a case reported by Denys. Since that time nosologists have shifted their point of view from the manifestation, *purpura*, to the manifestation, *reduction of blood platelets* in their attempt to arrive at a proper classification. This has led to the coining of a number of new names for the condition which no doubt will be discarded in turn, when the final etiology of the entity is arrived at. The disease probably occurs in mild form without the manifestation, reduced blood platelets, and without purpuric spots.

Wright made the observation in 1906 that blood platelets are derived from the pseudopodia of the megakaryocytes of the bone marrow. No one has successfully disputed this finding since that time and gradually it has been accepted. Much remains unknown, however, concerning the origin and physiology of these peculiar bodies.

In 1915 E. Frank⁵ arrived at the conclusion that the blood platelets are *always* reduced in purpura hemorrhagica and proposed the name "essential thrombopenia." In 1920 Eppinger⁶ suggested that essential thrombocytopenia was a better term as directly pointing

to reduction of the platelet cells rather than the substance thrombin. Hayem noted the extraordinary fact that there is an absence of clot retraction in primary purpura hemorrhagica. Duke⁸ in 1912 emphasized the prolonged bleeding time in the presence of a normal coagulation time in this disease.

Theories of pathogenesis of primary purpura hemorrhagica have been many and interesting. Certain French writers⁹ held that disturbances in hepatic function were primarily at fault. Grenet's work¹⁰ indicated that a toxic action on the central nervous system was the primary factor. The theory of infection has had many advocates. Giffin and Holloway¹² state: "There is a growing conviction that it (purpura) is usually secondary to localized infection and that in some way chemical toxins are formed as the result of bacterial action which affect the vascular tissue." They suggest that the process is not due to the direct action of a bacterium or its products, but to a secondary abortive substance originally designed to protect, the process probably being linked with protein intoxication.

Primary changes in the walls of the capillaries have been demonstrated in experimental purpura. In 1914 Ledingham¹⁹ produced purpura with hemorrhagic symptoms by injecting animals with antiblood-platelet serum. Bedson¹¹ concluded from observations on experimental purpura in 1922 that the two main factors concerned in the production of hemorrhages in purpura are: (1) Toxic action on the endothelium of bloodvessels; (2) removal of platelets from the circulation.

Recently Bedson¹³ has investigated the effect of splenectomy upon the blood platelets in experimental purpura. He states that splenectomy in guinea pigs gave rise to a great increase in the number of blood platelets in the blood stream. Blood platelets reached their highest level in ten to fourteen days and declined to normal in three or four weeks. Bedson concludes that splenectomy cannot be relied on to give any but temporary relief in the treatment of purpura hemorrhagica. This is especially important in view of the recent literature on splenectomy as a curative measure in purpura hemorrhagica.

Frank¹⁴ formulated a theory in 1915 that hemorrhages in primary purpura were due to an inhibitory action of the spleen on the bone marrow causing a reduction of the number of blood platelets in the circulation. Kaznelson¹⁶ agreed with Frank that the spleen was concerned in the reduction of blood platelets in hemorrhagic purpura but thought its action was a destructive one on the platelets after formation rather than an inhibition of proper formation. Brill and Rosenthal^{13, 41} have suggested that the entire so-called reticulo-endothelial system is concerned in the reduction of the number of blood platelets, the reticulo-endothelial tissue of the liver, lymph nodes and elsewhere participating as well as that of the spleen.

The treatment of primary purpura hemorrhagica has included

efforts by local and general styptic drugs to combat hemorrhages, injection of serum, injection of foreign protein, roentgen rays over the spleen and bone marrow, and recently the operation of splenectomy. In 1916 Kaznelson¹⁶ reported brilliant results following splenectomy in a case of thrombocytopenic purpura hemorrhagica. Since that time approximately 50 patients^{13, 42} have been splenectomized for this condition in various parts of the world. The majority of these reports are confirmatory of the value of this procedure.

Case Report.—E. M., aged eighteen years, a school girl, was admitted to the Pennsylvania Hospital, Philadelphia, on November 4, 1924, on the service of Dr. Charles F. Mitchell. Her chief complaint was bleeding from the vagina and gums. For the past ten months she had felt generally weak and had been told by relatives that she was pale. For the past two months she had been bleeding at intervals small amounts from the gums; and for the past five weeks she had been bleeding from the vagina. About a month before admission a large number of purpuric spots appeared on the skin. These lasted for a long time but disappeared. Her appetite was poor. Her bowels were constipated. She had had repeated attacks of sore throat during the past few years.

Physical Examination. The patient is a well-developed, well-nourished girl, but very pale and seems to be extremely anemic. Bleeding from the gums is the only positive finding about the head. There is no adenopathy. Examination of the lungs shows nothing abnormal. The heart is negative except for a soft systolic murmur at the apex. The spleen and liver are not felt and there are no masses or areas of tenderness. She is bleeding and passing clots from the vagina.

On account of the possibility of incomplete abortion, a dilatation and curettage was done on the day of admission. Blood clots were evacuated, but the patient continued to bleed. There was no evidence on examination of curettings of an abortion.

Shortly after this a diagnosis was made of purpura hemorrhagica.

Dr. George W. Norris made the following note on consultation on November 12: "Blood-pressure 117/55. Small pea-sized pale bluish-red petechial spots on left groin. Several brownish spots on back, smaller and may have had similar origin. Constriction of brachial vessels by blood-pressure cuff for about two minutes sufficient to cut off circulation has not produced petechia. Several petechial spots over right inner lower biceps region. Pain and tenderness right lower abdomen. Spleen not felt, not enlarged to percussion. Lungs clear. Heart not enlarged. Soft low pitched systolic murmur at apex of heart. Liver not felt except in epigastric notch. I believe this is a case of purpura hemorrhagica and in view of recent literature, splenectomy might be considered."

Course of Disease. On November 12: Transfusion—300 cc whole blood, direct method. The patient continued to bleed. The

transfusion improved her general condition but she did not stop bleeding from vagina. The bleeding from the gums has practically stopped.

November 15: Transfusion two hours before operation of 475 cc of whole blood. The spleen was removed. It was found to be somewhat enlarged and adherent to the diaphragm. The tail of the pancreas was also adherent near the hilus of the spleen. There was very little oozing. The patient's pulse became quite rapid during the operation, reaching 170 per minute but remained of fair volume. She reacted well from the operation.

She was considered to be in such good condition after coming out of ether that a postoperative transfusion was not done.

November 17: Given 35 cc of whole blood intramuscularly. The patient has continued to bleed from the vagina since operation about the same as before. Bleeding from the gums has ceased.

November 19: Transfusion of 400 cc of blood.

The patient's general condition improved after each transfusion but bleeding continued from the vagina.

November 21: The uterus packed with gauze soaked in thromboplastin.

November 21: Several small purpuric spots have appeared under the left breast.

November 22: Bleeding has stopped from vagina since packing.

November 22: 700 cc whole blood transfused.

November 23: Her temperature has risen to 106° F. (rectal), pulse 120. No bleeding from uterus.

November 24: Her temperature rose this P.M. to 105° F. (rectal); pulse rate 120. There is a systolic murmur at the apex; the abdomen is soft, with no tender points, or masses. The operative incision is in excellent condition. She has been incontinent all day, passing bowel movements and urine in bed frequently.

November 28: Great numbers of purpuric spots have appeared over the whole body. The tourniquet test is positive. There is no bleeding from the uterus, and most of the packing has been removed. The patient is extremely anemic and the effect of blood transfusion lasts but a day or two.

November 29: Transfusion of 400 cc of citrated blood did not produce a reaction and the patient died shortly after.

Laboratory Work. The Wassermann test was negative. Analyses of urine showed albumin present, varying from a trace to a heavy cloud, with no sugar or casts. Both aërobic and anaërobic blood cultures were made. On November 12 blood cultures were negative. On November 28 a rod-shaped organism was seen in a Wright's stain of the blood. Blood cultures taken immediately showed the *Bacillus fecalis alkaligenes* in both aërobic and anaërobic cultures. It may be interesting here to note that this organism was found also postmortem in cultures from the vena cava.

Clotting time on November 7 was seven minutes. On November

17 it was four minutes; November 28, four minutes. Oxidase stains made both before and after operation showed the abnormal mononuclear cells present to belong to the myeloblastic series. The red blood cells both before and after operation showed polychromatophilia, some poikilocytosis and anisocytosis and occasional stippling.

Examination of the feces was negative except for a strong reaction for occult blood. There was no frank bleeding from the lower bowel.

Bleeding time on November 7 was twenty minutes; on November 15, thirty minutes; on November 17, four minutes; on November 27, twenty minutes.

Clot retraction was absent both before and after operation. The blood when allowed to remain several days in the ice box showed no retraction of clot.

BLOOD COUNTS.

Date.	Red blood cells, millions.	Hemoglobin, per cent.
November 4	3,000	35
November 7	1,160	25
November 11	0,945	25
November 16	1,270	25
November 17	1,035	25
November 18	1,043	25
November 19	0,786	20
November 21	0,730	20
November 24	1,650	
November 26	1,480	25
November 28	1,100	20

WHITE BLOOD CELL COUNTS.

Date.	Total count, per c.mm.	Differential count in per cent.						Nucleated reds per c.mm.
		Poly.	Lym- pho.	L. M.	Tr.	Eos.	Myelo- cytes.	
November 4	9,600	31	32	2	4	0	31	0
November 7	5,200	33	28	2	1	0	36	Occasional
November 10	9,400	27	8	4	1	0	54	0
November 17	40,000	56	4	2	3	0	35	45,000
November 18	37,000	50	7	1	2	0	40	43,000
November 19	54,000	43	7	1	0	0	49	36,000
November 20	34,000	52	1	0	2	0	45	Many
November 21	20,400	45	10	2	1	0	42	47,000
November 22	23,236	46	9	0	0	0	45	39,564
November 23	55,000	42	3	0	0	0	55	105,000
November 24	24,950	66	3	2	1	0	28	80,850
November 26	36,000	90	2	0	0	0	8	24,000
November 28	53,000	62	2	0	0	0	36	7,200

BLOOD PLATELET COUNTS.

Date.	Per c.mm.
November 11	40,000
November 14	30,000
November 16	80,000
November 17	70,000
November 18	70,000
November 19	64,000
November 24	90,000
November 26	130,000

Examination of Spleen Removed at Operation. The spleen is moderately enlarged, weighing 190 gm. Its surface is smooth and glistening. The capsule does not appear to be thickened. The cut surface is uniform in color. There are no gross nodules or areas of localized involvement. The pulp is of a brick red color and lies even with the cut surface. The reticulum grossly shows no apparent increase in amount.

Microscopic sections show no thickening of the capsule. The trabeculae are prominent and distinct but there is no evidence of increased amount of fibrous tissue in the spleen. The germinal centers are distinct. The blood spaces are filled with cells having the morphological appearance of myeloblasts and myelocytes. The arrangement or lack of arrangement of these cells suggests that they are transient cells. There is no evidence of the uniform hyperplasia of cells *in situ* with destruction of architecture so characteristic of the myeloid hyperplasia of myelogenous leukemia. The lymphocytes and lymphoblastic cells of the germinal centers show no evident deviation from normal morphology. No blood platelets can be distinguished.

Postmortem Findings. (Dr. J. R. Paul.) The body is that of a well-developed and well-nourished young Italian girl. There is a very marked pallor of the skin and mucous membranes. Scattered over the chest and abdomen are showers of purpuric and ecchymotic spots. These are present over the breasts, upper abdomen and anterior surface of the arms. The legs are more or less free from these spots although there are two present over the femoral triangle on both sides. There is a recent "T"-shaped surgical incision in the left middle quadrant of the abdomen (both arms measuring about 15 cm. in length). It is fairly well healed but the edges are hemorrhagic and serum oozes from it.

The examination is confined to the surgical incision.

Peritoneal Cavity: On opening the peritoneal cavity it is found to be free from blood, although parietal and visceral peritoneum are studded here and there with tiny ecchymotic spots. An extremely interesting condition is encountered in that there is a well-developed sac of peritoneum situated on the left side of the peritoneal cavity, the orifice of which is opposite to Treitz's fossa. Fully two-thirds of the small bowel is loosely enclosed in this sac. As the duodenum and jejunum emerge from Treitz's fossa they enter this sac and the gut in this region is small, extremely pale and collapsed. Its contents are small in quantity and pale pink. In striking contrast is the appearance of the small gut as it emerges from the sac. It becomes distended, the walls are extremely dark and the contents dark red. There is no evidence of incarceration or strangulation. The colon is somewhat dilated throughout. All of the mesenteric lymph nodes are tremendously enlarged and edematous, some are cherry red in color, others are pale red, varying

in size from that of a pea to an olive. This includes the glands in the mesentery, about the celiac axis and along the spinal column. In contrast the glands in the pubic region and mediastinum are not enlarged. In the region of the splenic flexure (spleen removed) there is a large collection of broken down blood. Most of it seems to be retroperitoneal in location and situated about the tail of the pancreas.

The lungs and heart are examined through the diaphragm.

Heart: Definite cardiac hypertrophy is present.

Lungs: Pulmonary edema, mild in extent is present in both lower lobes.

Stomach, Duodenum, Pancreas: No gross changes noted.

Intestines: As noted above.

Liver: The liver is of normal size and appearance except for pallor.

Adrenals: The adrenals are small and pale orange in color. No hemorrhages.

Kidneys: Both kidneys present the same picture. They are quite large. The surfaces are smooth and pale. On section the cortex is found to be quite thick, extremely pale and the renal architecture poorly defined. The picture is that either of extreme anemia, or acute parenchymatous degeneration and infiltration of white cells.

Pelvic Organs: The uterus is small and of normal shape and size. It is dark red in color. The walls and cervix are soft. On exposing the uterine cavity a dark semigangrenous endometritis is encountered. Both ovaries are enlarged. The tubes are normal. The bladder is normal.

Autopsy Sections. Pancreas: The islands appear to be somewhat hypertrophied. The capillaries and other blood spaces contain blood showing many myeloblastic cells and nucleated red cells. No other noteworthy changes.

Liver: The capsule shows no changes. The liver cells appear shrunken. Some contain fat droplets. The capillaries are dilated and contain blood with a high percentage of myeloblastic cells. There is an occasional small area of perivascular exudation of cells of the same type seen in the blood stream. These resemble more an inflammatory reaction than the infiltrative areas usually encountered in leukemia.

Adrenals: Section is not remarkable. Bloodvessels contain myeloblastic cells.

Kidneys: Sections show very few changes except cloudy swelling of the tubular epithelium. The glomeruli, bloodvessels and interstitial tissue are not particularly abnormal in appearance. There are no focal collections of cells.

Small Intestine from Hernial Sac: The changes are not striking.

Several dilated lymphatics are present in the submucosa. The bloodvessels are dilated with myeloid cells.

Uterus: Sections show erosion of the mucosa with congestion and vacuolization of the epithelial cells of the glandular acini. The uterine veins are dilated and in places filled with plugs of blood and fibrin containing large numbers of polymorphonuclear and myeloblastic cells. There is no definite infiltration of interstitial structures with myeloblastic cells.

Mesenteric Lymph Node: The capsule is not thickened. The architecture of the node is largely preserved. There is marked edema. The marginal and septal sinuses are filled with red blood cells, nucleated red cells, myeloblasts and lymphocytes with a few large phagocytic cells enclosing red cells, mononuclear cells and debris. The pulp shows the same picture as that detailed above except for more abundant fixed cells of lymphocytic type. The uniform hypertrophy of abnormal cells seen in the leukemias is not present.

Bone Marrow: The bone marrow is quite cellular. There is no evidence of fatty infiltration or replacement. The cells are largely myeloblasts, erythroblasts and occasionally megakaryocytes, with some red blood cells containing no nuclei. Occasional phagocytic cells are seen containing ingested debris and cells. The impression one gets is that the mother cells of both the red cells and the polymorphonuclear cells are quite active and hyperplastic.

Summary of Findings. An eighteen year old girl was admitted to the hospital with a history of purpuric spots on the skin two months previously. Purpuric spots were present during stay in hospital and constriction of arm with blood-pressure cuff produced purpuric spots. For two months before admission she had been bleeding small amounts from the gums. For five weeks before admission she bled more or less continuously from the vagina. She developed extreme anemia but her general nutrition remained good and there was very little emaciation. None of the superficial lymph nodes were enlarged. The spleen was not particularly enlarged. There were no signs of cardiac or pulmonary disease or evidence of localized infection.

Bleeding time was prolonged. There was marked reduction of blood platelets. Coagulation time was normal. Clot retraction was absent. Anemia was profound. Before blood transfusion 3 counts of white blood cells ranged from 5200 to 9600; a differential count showed myeloblasts and myelocytes present. These were interpreted as a symptomatic myeloblastic stimulation from strain of repeated hemorrhages on bone marrow.

A splenectomy was done after preliminary blood transfusion.

Following splenectomy the patient ceased to bleed from gums. Vaginal bleeding continued until the uterine cavity was packed. After operation repeated transfusion of whole blood was done. The

effect of raising the hemoglobin and red cell content of the blood was only temporary, though there was no gross evidence of red cell destruction such as jaundice.

The patient died apparently of anemia and exhaustion despite repeated transfusions. After splenectomy there was an enormous increase of nucleated red cells with a large number of leukocytes of myeloblastic origin.

Discussion. The question of the proper diagnosis of this case presents some difficulty even in the presence of fairly detailed clinical history, laboratory results and postmortem findings. The patient presented the cardinal signs and symptoms of thrombocytopenic purpura: (1) Purpuric eruption; (2) hemorrhages from gums and vagina; (3) marked anemia; (4) prostration; (5) absence of a definitely localized area of disease to account for the condition; (6) prolonged bleeding time; (7) normal coagulation time; (8) marked diminution of blood platelets; (9) absence of clot retraction.

The unusual feature, however, was the presence of myelocytes and promyelocytes in fairly large relative proportion.

Ordway and Gorham⁴⁸ state: "A diagnosis of acute myelogenous leukemia in order to be above criticism must be substantiated by proof of the following points: (1) An aleukemic or subleukemic stage; (2) an acute downward course with death usually in from one to four months; (3) the characteristic picture of myeloblasts and myelocytes with transition forms between the two; (4) typical gross and histological findings in the liver, spleen, bone marrow and lymph glands; (5) specific proof of myeloid elements by enzyme reactions (oxidase stains)."

In regard to Item 4 they say: "A slight myeloid change is not sufficient proof. It must be a marked transformation since mild proliferation of myeloid tissue is not uncommon in severe anemias. The possibility of error in failing to insist upon this point is well illustrated by Naegeli."⁴⁷

Myeloid changes in the tissues of the case under discussion were not striking. The picture was not at all typical of the usual myeloid hyperplasia of leukemia. The myelocytes and myeloblasts present in the kidney, spleen, lymph nodes and liver were largely contained in bloodvessels and blood spaces. The uniform hyperplasia of myeloblasts in the enlarged lymph nodes with destruction of architecture so characteristic of the leukemias was entirely lacking. Stimulation myelocytosis in severe anemias, especially acute and subacute types of severe anemias, is a comparatively common finding. Examples might be multiplied of this type of myelocytosis in severe anemias with subsequent complete recovery of the patient.

We have felt, therefore, that it is impossible to classify the case as acute myelogenous leukemia and feel that the case was one of

severe essential thrombocytopenic purpura with marked stimulation myelocytosis.

Consideration of the question of why the patient failed to recover after splenectomy is of speculative interest and may afford some practical points. Transfusion of blood was not done immediately after the operation. Brill and Rosenthal consider that blood transfusion should immediately precede and follow the operation. It was not immediately done after operation by us because of the apparently good condition of the patient and because we considered the transfusion immediately preceding the operation to have been sufficient.

After operation the patient stopped bleeding from the gums, but continued to bleed from the vagina until the uterus was packed. It is possible that local measures to control vaginal bleeding should have been taken earlier. We hesitated to do this because of the danger of infection and because we hoped day after day that bleeding from the uterus would stop.

The theory of Brill and Rosenthal⁴¹ that the entire reticulo-endothelial system is involved in platelet destruction, that in the lymph nodes, liver, and elsewhere as well as the spleen, calls up the speculation as to whether in very severe cases such as the one under discussion, sufficient of the offending system is not removed by splenectomy to stop the process.

The finding of the jejunal hernia is of interest. Its significance is not apparent. While the patient had no clinical signs of intestinal obstruction the well known intensity of reaction from the absorption of toxic products from an obstruction to the higher portions of the bowel makes this fact of the hernia of enough speculative interest to be mentioned in a discussion of the case. It is possible that the immediate origin of the organism isolated from the blood (*Bacillus alkaligenes*) was from the partially imprisoned loop of small bowel, and that the retrogression following the temporary post-operative improvement may have been due to absorption of toxins from this area. Certainly the microscopic appearance of the mesenteric lymph node lends support to this view.

As we watched the blood picture from day to day we were struck by the profound struggles of the bone marrow to replace red blood cells in the circulation, as witnessed by the enormous numbers of nucleated red blood cells. Lenoble⁴⁴ believed he had discovered a new form to which he gave the name of myeloid purpura. This was characterized by the presence of a considerable number of normoblasts in the circulating blood. In the acute stage of the disease the number varied between 165 and 1250 per c.mm. In 1 case he found 3000 per c.mm. Sometimes according to Lenoble, neutrophilic myelocytes and more rarely eosinophilic myelocytes are found in the blood during a myeloid reaction. Labbé and Ameuille⁴⁵ concluded from their study that there was nothing specific

in the myeloid reaction. It varied with the extent of the hemorrhage and disappeared when bleeding ceased.

The number of nucleated red blood cells in our case after splenectomy reached the enormous number of 105,000 per c.mm. We have not found in the literature any case approaching this figure. Before splenectomy was done there were only a few nucleated red cells although the anemia was almost as profound at times before operation as after it. It certainly seemed that removal of the spleen profoundly stimulated the formation of young red blood cells either directly or indirectly. Examination of the blood count chart shows that the blood platelets were increased over the former figure after the removal of the spleen. There was a temporary reduction of the bleeding time. Bleeding from the gums ceased immediately after the operation. The total number of leukocytes was increased. This is usual after splenectomy. For a time the patient appeared to be improved clinically.

Transfusion of whole blood in our case appeared to be a useless measure to control bleeding. It was of value in temporarily raising the content of red blood cells and hemoglobin in the circulation.

Operation was approached in the case of the patient here recorded with a certain degree of confidence, our feeling being that if the patient survived the operative procedure we might expect a cessation of her hemorrhagic symptoms. We were disappointed. The patient made a good recovery from a surgical viewpoint after the removal of the spleen and evidence of stimulation of the functions of the blood forming organs was evident after operation but this was not sufficient for recovery.

We are aware of the fact that the final diagnosis in this case is somewhat problematical and that some may be inclined to consider it acute myelogenous leukemia with purpuric features. We have no desire to be dogmatic in our diagnosis. The bulk of the evidence appears to us to place the case as one of primary purpura hemorrhagica with stimulation myelocytosis. But we are quite willing to recognize that we may have the clinical entity hemorrhagic purpura merging in various degrees into the equally poorly limited field of leukemia.

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WASSERMANN-FAST SYPHILITICS TREATED WITH BISMUTH.

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WE propose in this article to show that bismuth has a real therapeutic value in reducing the "positiveness" of the Wassermann reaction or rendering it negative in the so-called "Wassermann-fast" patients. The term "Wassermann-fast" is restricted to those patients who have had one or more routine courses of arsphenamin and mercury without any appreciable reduction in the blood Was-

sermann. After a review of the literature up to this time we have been unable to find a series of such cases reported. It may be stated that each patient in this series had a negative lumbar puncture prior to bismuth therapy. Each patient has had a urinalysis before the institution of bismuth injections and subsequent monthly analyses during their treatment.

The epoch making work of Sazerac and Levaditi¹ in 1921 on the treatment of rabbit syphilis with bismuth heralded a new drug to the armamentarium of the therapy of syphilis. Soon after came the reports of Fournier and Guenot² on their clinical observations of 200 human syphilitics in all stages treated by this new antisyphilitic agent.

Syphilographers in all countries began experimenting with the various bismuth preparations. We soon learned that bismuth would cause cicatrization of the chancre and the disappearance of the concomitant adenopathy; regression of all secondary and tertiary manifestations with almost the same rapidity as the arsenical preparations; the Wassermann test in the preserologic period could be controlled and, if positive, could be reduced or rendered negative.

We also have learned that patients reacting unfavorably to arsphenamin will tolerate bismuth without the slightest difficulty. There are cases on record of patients whose symptoms have actively recurred while under arsenical treatment only to clear up with bismuth. Other cases have been reported in which both mucous membrane and cutaneous lesions have failed to disappear after vigorous arsenical and mercurial treatment, but responded quickly and favorably to bismuth.

One of us, who first used bismuth in this country on human syphilis, noticed that a few patients who were Wassermann-fast following intensive arsenical and mercurial treatment soon reacted with negative test when bismuth was used. Other writers about this time reported an occasional case responding similarly. We, therefore, decided to treat a series of patients with bismuth who were Wassermann-fast subsequent to intensive arsenical and mercurial treatment in order to ascertain whether the occasional cases reported were mere coincidences or whether we were dealing with a drug which had a definite therapeutic action in influencing the Wassermann reaction.

We selected our patients for this work in the order in which they came to the clinic. Each patient has had a complete physical, neurological, blood Wassermann, spinal fluid serology and urinalysis done before the beginning of bismuth therapy. All of these patients treated may be regarded as purely asymptomatic syphilitics with only a positive blood Wassermann test. No patient was selected who showed any trace of a positive spinal fluid in either cells, globulin, Wassermann test or colloidal gold.

BLOOD WASSERMANN TEST

Case No.	Number of doses of intravenous arsphenamin.	Number of mercurial injections.	Date.	Before treatment, blood Wassermann test.	After first course of 16 bismuth injections.	After second course of 16 bismuth injections.	After third course of 16 bismuth injections.	Albumin in urine.	Remarks.
399	67	60	1920-1923	++++	=	-	-	Negative	Feels fine.
353	51	41	1921-1923	++++	++++	++++	++	Negative	
272	59	71	1920-1923	++++	++++	+	+	Negative	Says "he never felt better."
105	50	63	1920-1923	++++	=	++	Negative	
450	31	28	1922-1924	++++	++++	++++	(+) negative	Negative	During first course of bismuth legs weak; arms painful. Later preferred bismuth to any other form of treatment.
367	31	31	1922-1923	++++	-	-	+	Negative	
1182	30	20	1916-1923	++++	=	=	Negative	
240	34	41	1922-1923	++++	+	=	-	Negative	Feels fine.
196	47	42	1922-1923	++++	=	Negative	
92	32	38	1922-1924	++++	++	=	++++	Negative	
1320	39 Mixed treatment—pills, etc. Private treatment for three years.	20	1924	++++	-	++++	++	First course of bismuth reduced blood to complete negative for first time in five years.
115	27	30	1922-1923	++++	-	-	Negative	
328	32	18	1921-1924	++++	-	-	Negative	
291	63	75	1918-1923	++++	=	Stopped in — midst of this course	Negative	

939	26	20	1919-1923	++	-	-	+	Negative	Pain in back—sleepy—tired.
270	46	82	+	≠	≠	≠	Trace after first course	
254	37	40	1922-1923	++++	++++	++++	++++	++++	Faint trace after first course, cleared up later	
122	42	60	1922-1923	++++	++++	++++	++++	Incomplete	Negative	
635	52	77	1919-1923	++++	++++	++++	++++	++++ chol. = alc.	Faint trace after second course—negative third	
502	17	20	1922-1923	++++	After 7 bismuth injections W. R. +++++	Negative	After first injection developed urticaria arms and legs. After second injection developed maculo-papular rash. Pains in legs. Bismuth stopped after seventh injection.
253	32	50	1922-1923	++++	++++	Negative	
1154	15	17	1923-1924	++++	++++	++	++	Negative	
551	19	17	1922-1923	++++	++++	Negative	
507	27	16	1922-1923	++++	++++	++++	++++	Negative	
107	29	20	1919-1923	++++	++++	++	++	Difficulty with arsphenamin and mercury. Faint trace albumin in urine after fifth injection. Off of treatment for two weeks. Urine showed few fine granular casts. Stopped treatment for two months. Began treatment again but only a faint trace showed.

Summary of Findings. There were 25 patients treated in our series all of whom have been under bismuth therapy for one year. Each patient has received bismuth intramuscularly twice weekly until 16 injections have been given. This constitutes one course after which all treatment was suspended for one month at the end of which time a blood Wassermann was made.

In each patient, as the chart shows, the blood Wassermann was 4+ with the exception of 4 patients, 2 of whom were 3+, 1, 2+, and 1, 1+, respectively.

After the first course of bismuth therapy, 11 patients out of 25 (44 per cent) gave a negative or plus-minus Wassermann reaction; 9 were unchanged (36 per cent) and 5 were either slightly reduced or reduced to 1+ (20 per cent). In other words in 64 per cent of the cases the Wassermann reaction was improved or rendered negative by bismuth after remaining unchanged for one or more years of arsphenamin and mercurial therapy.

Following the second course the serology was further improved. However, only 21 patients continued their treatment. Of this number 14 were serologically improved or remained negative ($66\frac{2}{3}$ per cent); 5 were unchanged from their previous status (23.8 per cent) and 2 had reverted from plus-minus to 2+ and negative to 3+ respectively (9.5 per cent). There was a further improvement after this course over the first course of $22\frac{2}{3}$ per cent; opposed to 9.5 per cent relapse.

Only 11 patients finished the third course. Of this number 7 remained negative or were further improved (63.6 per cent); 1 remained unchanged (9.09 per cent) and 2 reverted, 1 from negative to 1+ and 1 from plus-minus to 3+ (18.1 per cent). One course was incomplete.

The average percentage of improvement or negative serology after three full courses of bismuth was 64.7. The percentage of unchanged Wassermann reactions from the original after three full courses was 22.96. The percentage of reversions after the second and third courses was 13.8.

It has been stated at various times that bismuth was prone to produce an albuminuria. A glance at the chart does not bear out these statements. We observed a faint trace in only 4 cases which cleared up before the third course except in 1 patient in whom the trace persisted throughout.

It might be appropriate here to say that in only 1 patient did we observe any cutaneous eruption which cleared up quickly after withdrawal of all treatment. We had no cases of stomatitis nor any untoward symptoms excepting an occasional tenderness where the injections were made. However, these were not more painful than mercury and some patients preferred bismuth to mercury. We frequently saw gingival pigmentation but this was of no moment.

Conclusion. We believe that bismuth has a real and lasting place in treating Wassermann-fast syphilitics. In view of the fact that the Wassermann has remained negative for nearly a year or more in a large percentage of our patients, we believe that the permanency of this reduction cannot be denied. However, a greater length of time is required, free from all treatment, before we can definitely affirm this permanency of the reaction.

1. Bismuth should be given in all Wassermann-fast syphilitics.
2. Albuminuria is not produced more frequently with bismuth than with other antisyphilitic agents.
3. No untoward effects are met with in bismuth therapy when properly administered.

We desire to thank Dr. D. D. Stetson for permitting us to carry out this work in his service. To Dr. Randal Hoyt we express our thanks for performing the lumbar punctures and making the neurological examinations. We express thanks to Dr. D. S. Jessup for the urinalyses and to Dr. Frederick Fox for doing the serology. Both alcoholic and cholesterinized antigens as well as water-bath and ice-box fixations were done on all Wassermans. The preparation used in this work was potassium and sodium tartrobismuthate.

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THE WASSERMANN REACTION IN THE BLOOD AND SPINAL FLUID OF PARETIC NEUROSYPHILIS.

WITH THE PRESENTATION OF THE RESULTS IN ONE HUNDRED AND SIXTY-SIX CONSECUTIVE HOSPITALIZED CASES.

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The purposes of this paper are: (1) To discuss the frequency of a positive Wassermann reaction in the blood as compared to

a positive reaction in the spinal fluid in paretic neurosyphilis, and (2) to discuss the frequency of a negative spinal fluid in paretic neurosyphilis.

I. Findings in the Present Series. The findings of the Wassermann reaction in a series of 166 consecutive cases of general paralysis are presented, taken from the records of the Boston Psychopathic Hospital in 1919, with the permission of the Director, the late Dr. E. E. Southard.* Symptomatalogical analysis of these 166 cases has been presented elsewhere.¹

In this series of 166 cases there were 3 in which the Wassermann was not done; in 143 cases it was performed on both the blood and spinal fluid; in 11 cases only on the blood; in 9 cases only on the spinal fluid. The results follow:

Blood Wassermann performed in 154 cases, with 137 positive reactions.

Spinal fluid Wassermann performed in 152 cases, with 143 positive reactions. Hence, in 154 cases clinically diagnosed general paralysis 90.1 per cent showed a positive blood Wassermann reaction, while 94.8 per cent of 152 cases gave a positive spinal fluid reaction, indicating in this series that the spinal fluid Wassermann reaction is positive more frequently than the blood Wassermann.

Comparison of the serum and spinal fluid results in the 143 cases in which blood and spinal fluid Wassermann tests were performed is made in Table I.

TABLE I.

Number of cases.	Blood serum.	Spinal fluid.	Per cent.
124	Positive	Positive	86.7
5	Positive	Negative	3.4
11	Negative	Positive	7.6
3	Negative	Negative	2.2

From these data it may be noted that 9.8 per cent of 143 cases had a negative Wassermann test on the blood and 5.6 per cent a negative test on the spinal fluid.

II. Frequency of Positive Serum and Spinal Fluid Reactions. There is considerable disagreement at the present time on the frequency of the occurrence of a positive Wassermann reaction in the blood in general paralysis as compared with its frequency in the spinal fluid. Many workers have found the spinal fluid to give a higher percentage of positive reactions than the serum, as has occurred in the present series detailed above. Boyd² states that it is always positive in the fluid, and also states that it is very rare for the reaction to be positive in the serum and negative in the fluid. Eskuchen³ has recently published his results in 346 cases of syphilis of the central nervous system, in which he found

* The permission of the present director, Dr. C. Macfie Campbell, was also secured for the publication of these data.

97 cases which gave a negative blood reaction and a positive spinal fluid reaction. Of 72 cases of general paralysis, 5.5 per cent gave a negative blood and a positive spinal fluid Wassermann reaction. Kafka,⁴ in a series of 124 cases of general paralysis, found nearly 20 per cent which showed a positive spinal fluid and a negative serum Wassermann reaction. Eichelberg⁵ obtained positive tests in every spinal fluid of patients with general paralysis. Marie, Levaditi and Yamanouchi⁶ found 93 per cent positive reactions in the spinal fluids of 30 cases of general paralysis. Nonne,⁷ as quoted by Levinson, holds that if sufficient fluid is used the test is positive in all cases of syphilis of the central nervous system. Haguénau⁸ states that practically all authors admit that the Wassermann reaction is nearly always positive in the spinal fluid of general paralysis, and quotes a large number of workers to support this statement. Sicard⁹ has contended for nearly two decades that the spinal fluid in this condition is always positive, and still maintains this view. Sabatini¹⁰ states that even with treatment in his cases the fluid remains constantly and irreducibly positive. Cestan and Riser¹¹ in 40 cases found positive reactions in the fluid in every instance, although it was necessary to use very large quantities of the fluid in some. Smith and Candler,¹² in England, found 92.1 per cent positive Wassermann reactions in the fluid of 64 paretics. Rizzo¹³ believes the result of the Wassermann test of the spinal fluid is always of greater value than the result of the blood test. Darling and Newcomb¹⁴ found a positive Wassermann reaction in the spinal fluid of all paretics; while a positive reaction in the blood seemed the rule, repeated negative findings could not exclude the diagnosis of paresis. Marie and Levaditi¹⁵ found 73 per cent of 39 cases gave a positive reaction in the fluid compared to 59 per cent of 30 cases in the blood. And to cite other findings: Miller, Brush, Hammers and Felton¹⁶ found 98 per cent of 130 cases with a positive spinal fluid Wassermann reaction; Noguchi and Moore¹⁷ report 73 per cent in 60 cases; Wassermann and Plaut¹⁸ found 88 per cent in 41 cases; Morgenroth and Stertz,¹⁹ 100 per cent in 8 cases; Noguchi, Rosanoff and Wisemann,⁴⁶ 87.5 per cent in 56 cases. Fuchs²⁰ gives a series of 56 cases of latent syphilis showing no signs of nervous disease, but all with changes in the spinal fluid. Of a total of 131 cases examined, 29 per cent had negative blood Wassermann reactions, although all had changes of some kind in their spinal fluids. Fildes, Parnell and Maitland²¹ found the cerebrospinal fluid was abnormal in a series of 624 cases of syphilis in all stages, in which there was no clinical sign or symptom of nervous disease. Twenty-nine cases had over 100 cells per 1 c.mm. and 9 had over 300. Moleen²² cites several cases without signs or symptoms showing changes in the spinal fluid, including a positive Wassermann test.

TABLE II.—WORKERS FINDING POSITIVE SPINAL FLUID WASSERMANN TEST MORE CONSTANT THAN POSITIVE SERUM WASSERMANN.

Author.	Findings.
Wassermann and Plaut ¹⁸ 1906	41 cases with 88 per cent positive fluids.
Marie and Levaditi ¹⁵ 1907	39 cases, 73 per cent positive fluids and 59 per cent positive serums.
Morgenroth and Stertz ¹⁹ 1907	8 cases, all positive fluids.
Eichelberg ⁵ 1908	100 per cent positive spinal fluids.
Marie, Levaditi and Yamamoto ¹⁶ 1908	30 cases, 93 per cent positive fluids.
Noguchi and Moore ¹⁷ 1909	60 cases, 73 per cent positive fluids.
Smith and Candler ¹² 1909	64 cases, 92.1 per cent positive fluids.
Noguchi, Rosenoff and Wiseman ¹⁶ 1910	56 cases, 87.5 per cent positive fluids.
Darling and Newcomb ¹⁴ 1916	Positive fluid in all cases and serum usually positive.
Sabatini ¹⁰ 1918	Spinal fluid always positive.
Boyd ² 1920	Fluid always positive; rarely positive serum with negative fluid.
Haguenau ⁸ 1920	"Nearly always positive in fluid."
Kafka ⁴ 1920	20 per cent with positive fluids and negative serum.
Miller, Brush, Hammers, Felton ¹⁶ 1920	98 per cent of 130 cases with positive fluids.
Sicard ⁹ 1920	"Fluids always positive."
Cestan and Riser ¹¹ 1922	40 cases, all fluids positive.
Fuchs ²⁰ 1922	29 per cent of 131 cases of central nervous system syphilis with negative serum Wassermann.
Rizzo ¹³ 1922	"Fluid test of more value than serum test."
Eskuchen ³ 1923	72 cases, 5.5 per cent with positive fluid and negative serum.
Nonne ⁷ 1923	100 per cent of fluids positive with sufficient amount used.

On the other hand, there are many writers who hold that the serum usually presents a higher percentage of positive reactions than the spinal fluid. Boas²³ has reported 100 per cent positive serum reactions in a series of 243 cases, while he obtained only 94 per cent positive spinal fluid reactions in 201 cases. He points out that the majority of German workers find the serum more frequently positive, while the majority of French workers have found the fluid more constantly positive, and cites several on each side of the question. Craig²⁴ states that in paresis the Wassermann test is positive in the blood in nearly 100 per cent of the cases, and if sufficient spinal fluid is used it is positive in practically 100 per cent. Edel²⁵ found 100 per cent positive reactions in the serum in 62 cases. Plaut²⁶ found in 1420 cases none with negative blood and positive spinal fluid Wassermann reactions, although he noted 8 cases in which the reaction was negative in both the spinal fluid and the serum. Nonne and Holzmann²⁷ found 100 per cent positive reactions in the serum and nearly so in the fluid. Stertz²⁸ found 95 per cent of the spinal fluids gave a positive reaction, but asserted that the serum generally gives better results than the fluid. Marinescu²⁹ found 94 per cent of 35 cases gave positive Wassermann tests in the serum. Raviart, Breton and Petit³⁰

record 93 per cent of 72 cases with positive reactions in the serum, and Lesser³¹ found 100 per cent of 62 cases. There are workers who have found the Wassermann test positive in both the blood serum and the spinal fluid in practically all cases (Craig,²⁴ Plaut,²⁶ Nonne and Holzmänn,²⁷ McIntosh and Feldes³²).

TABLE III.—WORKERS FINDING POSITIVE SERUM WASSERMANN TEST MORE CONSTANT THAN POSITIVE SPINAL FLUID WASSERMANN.

Author.	Findings.
Edel ²⁵ 1908	62 cases, 100 per cent positive serums.
Lesser ³¹ 1908	62 cases, 100 per cent positive serum.
Raviart, Breton and Petit ³⁰ . . . 1908	72 cases, 93 per cent positive serum.
Stertz ²⁸ 1908	95 per cent positive fluid, and serum with better results than fluid.
Marinescu ²⁹ 1909	94 per cent of 35 cases with positive serum; fluids less.
Nonne and Holzmänn ²⁷ 1910	100 per cent positive serum and nearly so in fluid.
Plaut ²⁶ 1920	1050 cases, 42 cases with negative fluid and positive serum.
Craig ²⁴ 1921	100 per cent of serum positive and nearly 100 per cent of fluids.
Boas ²³ 1922	243 cases, 100 per cent positive serum and 94 per cent positive fluids.

III. Occurrence of Negative Wassermann Test in the Spinal Fluid in Paretic Neurosyphilis. From the above, it appears that a large number of workers have found a negative Wassermann test in the cerebrospinal fluid in some cases of general paralysis, varying from 1 to 2 up to as high as 27 per cent of the cases, the great majority being less than 10 per cent. It is generally recognized (Boyd,² Rizzo,¹³ Craig,²⁴ etc.) that the Wassermann reaction in the fluid in general paralysis is stronger and obtained with a less amount of the fluid than in any other syphilitic disease of the central nervous system, and this fact has been suggested as a point in differential diagnosis. However, apparently it is negative in certain cases, as for example in our own series there were 5.6 per cent of 143 cases which had a negative reaction in the fluid.

Despite the fact that in the past, as has been cited, many workers have reported a negative Wassermann reaction in a small but rather constant percentage of active cases of general paralysis, there is a variance of opinion as to whether the spinal fluid may be normal in the presence of active central nervous system syphilis. It is recognized that the Wassermann reaction may be negative while the fluid may show other signs of activity. However, Solomon and Klauder³³ state that the only type of neurosyphilis in which it is generally recognized that the spinal fluid may be negative is that in which the disease process, as far as the central nervous system is concerned, affects almost solely the bloodvessels—thrombosis, hemorrhage, cerebral aneurysm and arteritis obliterans. Hoaglund and Prioleau³⁴ report a large occipital gumma with

practically no changes in the spinal fluid and a negative Wassermann test.

Nonne³⁵ has classified into five groups the negative spinal fluids in neurosyphilitics:

1. The fluid is normal from the beginning, a rudimentary process.
2. The fluid begins as pathological but becomes normal, this being the case in healed syphilitic disease of the central nervous system.
3. The fluid shows improvement over its former condition but is still not entirely normal. In this condition the disease process is improved.
4. The fluid is still pathological as it was earlier, but the clinical picture has remained stationary.
5. The fluid remains pathological as it was formerly, with an increase in the disease process.

Solomon and Klauder³³ have added to this classification a sixth group in which the fluid may have no pathologic changes or very mild ones, and the disease be active and progressive, and cite as evidence active cases of tabes, cerebral gumma, cerebral syphilis of the type causing nerve palsies, Erb's syphilitic spastic paraplegia, syphilitic epilepsy, syphilitic paranoia and syphilitic dementia, all with negative spinal fluids. They agree that in many instances in which the evidence of a syphilitic nervous involvement is shown by the physical signs and the fluid is normal these signs present evidence of a former activity which has been halted. Wynn³⁶ has reported 2 cases of paresis in which the spinal fluid changes after treatment suggested improvement while there was no clinical evidences of improvement and there have been many references to similar observations in connection with the various recent treatment innovations. Fordyce and Rosen³⁷ have pointed out that the classical symptoms of tabes dorsalis may occur with a negative Wassermann reaction in spinal fluid and blood, and Thaysen³⁸ presents a series of 30 cases of tabes dorsalis developing with negative serum Wassermann tests, 7 cases of which also had negative spinal fluid Wassermann tests, and 5 of these 7 cases gave a definite history of syphilis. Dreyfus³⁹ has pointed out that 35 to 40 per cent of tertiary syphilitics with isolated pupillary abnormalities have negative Wassermann reactions in the spinal fluid, and the fluid remains negative after provocative arsphenamin injections. Wüllenweber⁴⁰ also found that a certain number of a series of 28 cases of syphilis showing only pupillary changes have a negative spinal fluid Wassermann test, and believes the prognosis better in these cases than in those where the fluid shows alterations. In Plaut's series of 1050 cases²⁶ of general paralysis in which both the serum and spinal fluid Wassermann tests had been done, there were 42 cases in which the fluid was negative, although the serum was positive. Boas²³ found 12 cases in a series of 201

of general paralysis (6 per cent) with a negative Wassermann test in the spinal fluid. In a series of 204 cases of neurosyphilis Worster-Drought, Fry and Lynch⁴¹ found 35 in which the clinical evidence of neurosyphilis was definite with the cerebrospinal fluid yielding a negative Wassermann reaction but a positive colloidal-gold curve. Of these 7 were "taboparesis," 3 with a positive Wassermann test in the blood serum, and 4 with a negative serum Wassermann. As has been mentioned, Stertz,²⁸ Marinescu,²⁹ Nonne,³⁵ Smith and Candler¹² and others have found a certain percentage of negative Wassermann reactions in the spinal fluid of active cases of general paresis. Targowla⁴² concluded from his study of the fluid in paresis that none of the various tests were specific, but must be taken together with the clinical picture to establish the diagnosis. We may safely state that there is a large group of workers who believe that the spinal fluid may have a negative Wassermann reaction in paretic neurosyphilis.

However, there are still many workers who agree with Ernest Jones,⁴³ when he summed up the knowledge concerning the sero-diagnosis of general paralysis in 1909, by stating that "A positive reaction in the cerebrospinal fluid is strongly indicative of a general paralysis, and a negative reaction is less strongly, but unquestionably indicative of its absence." Even more will agree with his statement that "A positive reaction in the blood of a suspected case of general paralysis is of some value in support of the diagnosis, and a negative reaction is of much greater value in excluding such a diagnosis." Boyd² states very positively that the Wassermann reaction in the spinal fluid of general paralytics is always positive, whereas it is negative in at least 70 per cent of cases of cerebrospinal syphilis with 0.2 cc of fluid. Nonne⁷ gives 100 per cent positive Wassermann reactions in the cerebrospinal fluid in general paralysis, tabes dorsalis and cerebrospinal syphilis if large quantities of the fluid are used. Craig²⁴ states that if 0.5 cc of fluid are used practically 98 per cent of cases of paresis will give a positive reaction in the spinal fluid, a result never found in any other condition of the central nervous system. Eichelberg⁵ found 100 per cent positive reactions in the fluid. As has been mentioned before, Sicard⁹ has long maintained that the fluid is always positive. Cestan and Riser¹¹ were able to obtain a positive reaction in the fluid in all of 40 cases, though in some it was necessary to use very large amounts of the fluid. Rizzo¹³ goes so far as to state that a positive Wassermann reaction in the spinal fluid is the only sure index of a neurosyphilitic lesion.

Craig²⁴ holds that this wide variety of opinion is due to failure to use sufficient amount of fluid. He states that "because of the use of too small amounts of spinal fluid in making the Wassermann test, much of our data regarding the occurrence of a positive reaction in the various syphilitic infections of the central nervous

system are worthless." He gives credit to Hauptmann and Hossli⁴⁴ as "the first to insist upon the use of a large quantity of cerebrospinal fluid in applying the Wassermann reaction and their work changed entirely the prevalent conception of the comparative rarity of a positive reaction in diseases like tabes, and demonstrated that almost any syphilitic disease of the central nervous system would give a positive Wassermann reaction with these larger amounts of fluid." In his own experience he finds that if 0.5 cc of spinal fluid is used in paresis practically 98 per cent will give a positive reaction, while if smaller amounts be used the percentage of positive results will be found to decline to about 75 per cent, or 80 per cent when 0.2 cc is used. Boyd² has also found the principle true, that larger amounts of fluid frequently give positive reactions where smaller amounts give negative reactions. As has been cited, Cestan and Riser¹¹ obtained 100 per cent positive reactions in the fluids of 40 cases of general paralysis, although in some instances they used 5 to 6 cc of the fluid in making the test. Hence there is strong evidence that most of the discrepancies which exist are due to failure to use sufficient amount of fluid in making the test. However, we believe that there is sufficient evidence from the work of reliable men that the spinal fluid may be entirely negative in the presence of active neurosyphilis, and that the Wassermann test may be negative in the spinal fluid in paretic neurosyphilis.

TABLE IV.—WORKERS NOTING 100 PER CENT POSITIVE SPINAL FLUID WASSERMANN REACTIONS IN PARETIC NEUROSYPHILIS.

Author.		Findings.
Eichelberg ⁵	1908	100 per cent of cases.
Darling and Newcomb ¹⁴	1916	Positive in all cases.
Sabatini ¹⁰	1918	Positive even after treatment.
Sicard ⁹	1918	"Always positive."
Boyd ²	1920	100 per cent in paresis; 70 per cent in cerebrospinal syphilis.
Craig ²⁴	1921	"Practically 98 per cent" if sufficient fluid is used.
Cestan and Riser ¹¹	1922	100 per cent positive in 40 cases.
Nonne ⁷	1923	100 per cent positive with sufficient fluid.
Rizzo ¹³	1923	Positive Wassermann only sure index of syphilis.

Another theoretical consideration regarding the occurrence of a positive and negative reaction with the Wassermann test in the fluid of syphilitics has been suggested by Eicke and Löwenberg,⁴⁵ who showed that after heating the fluid to 56° C. for half an hour and so inactivating it, weakly positive reactions became negative and other positive reactions became less strongly positive. Rizzo¹³ has pointed out that fluids from neurosyphilitics which give a positive Wassermann reaction when active, and a negative reaction

when inactivated, give in both states a positive colloidal benzoin reaction; in other words, the results of the two reactions are not parallel, which is also borne out by the findings of Worster-Drought, Fry and Lynch,⁴¹ cited above. Rizzo further states that the general paralytic spinal fluid does not present this phenomenon of thermolability; the intensity of the Wassermann reaction in the inactivated fluid of a general paralytic is the same or slightly less than that of the activated fluid and he considers this a differential diagnostic point.

Summary. 1. The majority of investigators have found the cerebrospinal fluid to give consistently a higher percentage of positive Wassermann reactions in paretic neurosyphilis than the blood serum, although many reliable workers have found a positive serum to be the more frequent.

2. In the present series in 154 cases clinically diagnosed general paresis 137 cases (90.1 per cent) showed a positive blood serum Wassermann test; of 152 cases the spinal fluid gave a positive Wassermann test in 143 (94.8 per cent).

3. In 143 cases both the serum and spinal fluid Wassermann tests were performed. Of this number both the spinal fluid and serum were positive in 124 cases (86.7 per cent); there were 5 cases with the blood positive and the spinal fluid negative (3.4 per cent); 11 cases with the blood negative and the spinal fluid positive (7.6 per cent); 3 cases with both the blood and spinal fluid negative (2.2 per cent).

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CONDITIONS SIMULATING ACUTE LYMPHATIC LEUKEMIA (INFECTIOUS MONONUCLEOSIS. TUBERCULOSIS).

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THE early diagnosis of acute lymphatic leukemia rests largely on the number, the relative proportions and the character of the white cells in the blood. It is important to recognize that other conditions may show blood changes so similar as to deceive the most expert observers. It is the purpose of this paper to record and discuss two such instances.

Case Reports. CASE I.—Acute Infectious Mononucleosis with Vincent's Angina. A white unmarried woman, aged twenty-six years, whose previous health and habits had been excellent and who had not been subject to upper respiratory infections, was taken ill on March 27, 1924, with a sore throat accompanied by headache, body pains, mild fever and prostration. On the fourth day of her illness, when I first saw her, the pharynx was congested, the tonsils being small and in no way abnormal. Two tender nodes the size of a pea were felt below the jaw on the left side, and there were a few shot-like, insensitive inguinal nodes. Otherwise, there was no enlargement of the superficial nodes. The heart and lungs were negative, neither the liver nor the spleen could be felt. The patient did not appear acutely ill. Her pulse and respiration were normal, and the temperature by mouth was 99.4° F. The symptoms suggested a mild pharyngitis. On the fourteenth day I was again called because she had not improved as expected. The patient had felt unable to go out and had spent a larger part of the time in bed. Her throat and neck had remained sore and she had continued having a little fever, up to 100.6° F. by mouth. The throat appeared about the same but the cervical glands were a little larger and more tender.

The spleen had become palpable. The blood was examined to exclude malaria and showed an amazing change; 12,500 white cells with 86 per cent mononuclears (78 per cent large mononuclears and 8 per cent small lymphocytes). A well-known hematologist was asked to examine this blood and he reported 15,000 white cells with 83 per cent mononuclears (including 41.5 per cent large mononuclears and 31 per cent small lymphocytes). The majority of these cells were distinctly abnormal, the predominating type being somewhat larger than the larger lymphocytes with pale blue cytoplasm and oval lobulated or kidney-shaped nucleus which stained intensely. (Fig. 1.)



FIG. 1.—Type of cell found in Case I.

On April 14, the nineteenth day of her illness, the patient entered Roosevelt Hospital and two days later was seen by an eminent medical consultant who considered acute lymphatic leukemia the most probable diagnosis. In the mean time smears had been sent to Dr. B. M. Randolph of Washington, the patient's family physician, and referred by him to Dr. Hunter of the George Washington University Pathological Laboratory. I am indebted both to Dr. Hunter and Dr. Randolph for this and subsequent blood examinations. Dr. Hunter did not think the slide showed leukemia and he could not identify any cells of marrow origin. An oxidase stain done at the Roosevelt Hospital on April 19 also failed to reveal marrow cells.

Immediately after her admission to the hospital, the patient's throat began to get definitely worse and the temperature rose steadily to nearly 104° F. Within three days, on the twenty-second day of her illness, a membrane formed on both tonsils with the typical appearance of Vincent's angina, a diagnosis which the

laboratory fully confirmed. At the same time there was an increase in the size and number of the glands, more becoming tender on both sides of the neck and some also becoming palpable in both axillæ. Radiograph made at this time showed nothing abnormal in either heart or lungs. The urine also was normal. Following two applications of arsphenamin to the throat there was a rapid improvement; the throat lesions cleared up; the temperature fell and the spleen diminished in size so that it could no longer be felt. By April 20, the twenty-fifth day of her illness, the patient was convalescent except that the glandular enlargement and the blood changes persisted unchanged until April 27, when she returned to Washington. On May 9, the leukocytes had fallen to 6400 but there were still 58 per cent mononuclears. On February 18, 1925, a final blood count showed 7000 leukocytes with 28 per cent mononuclears, only 3 per cent of which were of the abnormal type described above. Dr. Randolph reports an uneventful recovery and complete return to vigorous health. Tonsillectomy was performed in June, 1924.

TABLE I. BLOOD FINDINGS IN CASE I.

Date.	Hgb., per cent.	R. B. C. in mil- lions.	W. B. C. in thou- sands.	Neut.	Bas.	Eosin.	Lym- pho.	Large mono. and transit.	Pre myelo.†	Türk cells.	Count by.
1924.											
April 9	75	..	12.5	14	8	78	Self
April 11	78	4.690	15.1	12.5	3.5	1.0	31	41.5	Dr. Sondern
April 14	75	4.595	20.2	12	1	1	14*	72	Roosevelt Hospital
April 18	75	..	15.6	..	Differential			as above	Roosevelt Hospital
April 23	25	55	9	9	2	Dr. Hunter
April 26	12	48†	40	Self
May 2	38	55	2	2	1	Dr. Hunter
May 9	83	4.800	6.4	41	...	1	52	4	2	..	Dr. Hunter
Aug. 13	80	4.500	7.5	52	...	3	44	1	Dr. Hunter
1925.											
Feb. 18	85	4.350	7.0	68	1	3	25	3	Dr. Hunter

* In the proportion of 2 large to 12 small.

† In the proportion of 30 large to 18 small.

‡ On April 11 there were 8 per cent myelocytes and 2.5 per cent myeloblasts.

Acute infectious mononucleosis, glandular fever, or acute benign lymphoblastomatosis, of which the case just cited is an example, has aroused considerable interest in the past few years, because of epidemics, occurring chiefly in England, in which glandular swelling, sore throat and fever have been associated, in some cases, with a blood picture suggestive of leukemia. The first mention of an epidemic of glandular enlargement accompanied by fever was made by

E. Pfeiffer in 1889. This syndrome in the next few years was described quite generally under the term glandular fever, by Türk, West, Marchand, Cabot, Deussing and others. The most comprehensive reviews of the subject in recent years have been made by Tidy and Morley, who in 1921 brought the literature up to date, by Tidy and Daniel in 1923, and in this country by Longcope in 1922, Sprunt and Evans in 1920, Morse and Bloedorn and Houghton in 1921. Most of these authors believe in the identity of glandular fever and acute infectious mononucleosis.

The symptoms are mild fever and prostration lasting two to three weeks, a sore throat, without exudate on the tonsils, enlargement of the cervical glands regularly and of other superficial nodes occasionally, not infrequently a palpable spleen and often an increase of the leukocytes with a relative mononucleosis which may run as high as 34,000 white cells and 89 per cent mononuclears. (Longcope). The cytoplasm of these cells is greater in volume and more deeply staining than that of normal small lymphocytes. Their nuclei are irregular and frequently notched. Degenerating forms are absent in contrast to their frequency in acute lymphatic leukemia. With oxidase stain these cells do not show granules indicating marrow origin and hence are believed to be of lymphoid origin.

The cause of infectious mononucleosis is unknown. Some authors consider it a form of infection with the organism of Vincent, and the case here reported lends support to this view. Tarnow, in an extensive study of the blood of individuals suffering from a Vincent's throat, found that the mononuclear cells ranged from 5.6 per cent to 27.6 per cent. On the other hand many cases of Vincent's angina show nothing abnormal in the blood. It would be interesting to determine the reaction of the blood of animals infected with the Vincent's organisms, but unfortunately, the cultural characteristics of the spirillum makes this experimental work impractical. In one case reported by Sprunt and Evans, the patient showed a typical polymorphonuclear blood response to ordinary pyogenic infection a year after having an acute mononucleosis so the condition is not a peculiar individual response to ordinary infections. The prognosis of this condition is uniformly good.

CASE II.—Lymphocytosis with Tuberculosis. A colored girl, aged sixteen years, was admitted to Roosevelt Hospital on May 21, 1920, had been suffering from pain in the upper abdomen for eight months. For two days previous to admission her throat had been sore. There were no other symptoms. On examination she was well nourished and did not appear very ill. There was an ordinary follicular tonsillitis. Throat cultures were negative for diphtheria. The cervical and axillary nodes could just be felt but were not tender. Examination of heart, lungs and abdomen revealed nothing abnormal. The blood pressure was 110 over 70. The urine on four exami-

nations showed specific gravity ranging from 1012 to 1028, a trace of albumin, a few hyaline casts once and no sugar. The stools contained a little blood on two occasions; but no ova or parasites could be found. Rectal and vaginal examinations were negative. Radiographic examination of the chest showed a large node at the left hilus but nothing else abnormal. The blood Wassermann and Widal tests were negative. No tubercle bacilli were found in the sputum.

The remarkable blood findings are shown in Table II.

TABLE II. BLOOD FINDINGS IN CASE II.

Date.	Hgb., per cent.	R. B. C. in millions.	W. B. C. in thousands.	Mononuclear cells, per cent.
May 21	78	2.840	9.4	80
May 25	11.2	87
May 27	23.4	96
May 28	34.8	96
May 30	17.0	90
June 1	34.0	96
June 5	36.8	95½
June 7	29.9	95½
June 9	31.2	95½
June 13	22	1.144	8.6	96½
June 15	28	1.552	8.6	94½
June 17	24	1.212		95½
June 19	11.6	95
June 21	23.8	97
June 27	8.4	95½



FIG. 2.—Type of cell found in Case II.

The mononuclear cells were mostly large with horseshoe nuclei and devoid of cytoplasmic granules (Fig. 2); nor could any of these be shown after oxidase staining. No nucleated red cells were ever found. The patient had a persistent and increasing temperature.

and progressively lost flesh and strength. No other physical signs were found. She died on June 28, five weeks after admission. Three members of the attending staff concurred in the diagnosis of acute lymphatic leukemia. The autopsy showed tuberculous bronchopneumonia in the left upper lobe with tuberculosis of the tracheal and bronchial lymph nodes. Miliary tubercles were scattered through both lungs, the liver and the spleen. The marrow, studied both by smear and in sections, showed no pronounced abnormality.

This case, for which I am indebted to Dr. Rolfe Floyd, is an example of a much rarer condition than acute infectious mononucleosis. I have only found one other similar record, by Wiechmann in 1922, of a patient who died of miliary tuberculosis as shown by autopsy. Here, however, the mononuclears reached only 64 per cent.

There are many nonleukemic conditions where a distinct lymphocytosis is present, rarely however, so marked as to suggest a leukemia. In children, lymphocytosis is common in congenital syphilis, scurvy and rickets, and is characteristic of the blood picture in pertussis. In adults, lymphocytosis is associated with tuberculosis, malaria, hemophilia, typhoid, pellagra and other diseases. Increase in the number of lymphocytes has been reported in connection with the administration of thyroid extract, tuberculin, arsphenamin (Keidel and Moore in 1921) and pilocarpin. Minot and Smith (1921), reported abnormal types of leukocytes in tetrachlormethane poisoning. Cabot in 1913, pointed out the association of lymphocytosis in connection with streptococcic infections.

The blood of an acute leukemia may show a distinct preponderance of all small lymphocytes, such as makes up the blood of the great majority of chronic leukemias of lymphatic origin. On the other hand, the smear may show both a relative and absolute increase of the pathologically large mononuclear cells. It is this type of picture which causes such confusion and uncertainty in diagnosis. The so-called aleukemic leukemias, where the total leukocyte count is normal or subnormal, adds to the confusion, especially where there is no clue to the puzzle in a high proportionate number of lymphocytes. The prognosis of leukemia is uniformly bad and it is quite possible that such cases as have been reported by Ireland, Baetjer, Rührhah and B. Gutmann and others, as acute leukemia terminating in recovery, belong in reality in the category of infectious mononucleosis. It must be remembered that there has been no case reported in which a patient suffering from acute infectious mononucleosis has developed an acute leukemia. The important question of a possible relation between these two conditions is at present no more than a matter for speculation.

Summary. In view of the cases presented, a high absolute and relative mononuclear count, persistent fever, and enlarged lymph nodes are not enough to establish the diagnosis of acute lymphatic

leukemia. This diagnosis must wait on the progressive development of symptoms and until repeated blood examinations have demonstrated thoroughly typical blood changes.

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DIFFERENTIATION OF AMEBIC DYSENTERY FROM SO-CALLED IDIOPATHIC ULCERATIVE COLITIS.*

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AMEBIC dysentery, while common in tropical and subtropical regions, is considered rare in patients seen by physicians in the Middle West portion of the United States, excepting those where there has been a definite infection contracted in the warmer climates. This opinion exists in spite of the fact that there are reports of amebic dysentery on record from more than half of the United States, including Illinois and many northern states. These instances of *Entameba histolytica* infection observed in Chicago emphasize the need for physicians, here and in other parts of the North, to be mindful of this type of dysentery in examining patients with chronic ulcerative colitis. Smithies' report of amebic dysentery in patients examined in Chicago mentions 27. Because of such reason by exclusion, amebic dysentery in this latitude is not considered seriously

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when patients with ulcerative colitis are examined. Haughwout recently has expressed a similar opinion.

During the past six months amebic dysentery has been demonstrated in 6 patients at St. Luke's Hospital, Chicago. These observations emphasize the need of careful examinations for amebæ in patients having symptoms of ulcerative colitis, and also emphasize again that amebic dysentery is not uncommon in these parts of the country. Of the 6 patients observed, 4 were treated successfully with emetin hydrochlorid. In the other 2 the disease was not recognized clinically and the diagnosis was made after death by postmortem examination. With 1 of these 2 patients the dysentery was considered to be of unknown origin because cultures failed to demonstrate in the stools bacteria of the dysentery types, and other examinations were not successful in disclosing the amebæ. The dysentery symptoms with the other patient were masked by other intraabdominal ones, and the ulcerative lesions of the large bowel were not known to be present until demonstrated by the postmortem examination. Motile amebæ, with red cell inclusions, were found in the exudate present in the abscesses of the mucosa.

As regards the source of the amebic infections, some can be traced quite definitely to a transient visit to southern states, but others seem to have been acquired in the North. How the latter infections occur offers considerable speculative thought. Infection anywhere probably comes by ingesting contaminated food or water. Vegetables or fruit grown in the South and furnished in season or out of season may be the means whereby people in these parts become infected. There is, of course, the possibility that the *Entamoeba histolytica* is gradually being introduced into the northern climates and is adapting itself to the new environment. In this way the disease becomes endemic.

Report of Cases. CASE I.—C. M., a white man, aged thirty-four years, a salesman by occupation, was admitted to St. Luke's Hospital, February 14, 1924, because of diarrhea, flatulence, exhaustion, weakness and sleeplessness. The watery stools, which had commenced ten days previously and had often been as many as one per hour, were brown, contained blood, and their passage was accompanied by painful abdominal cramps.

Before the onset of the diarrhea, the patient had been well. Since then, he was unable to work but was not confined to his bed, and had been treated by his family physician, who gave him a milk diet and prescribed certain drugs without relief. The family and personal history of the patient are unimportant, excepting typhoid fever at the age of nine. As a traveling salesman, his territory included the northern parts of Illinois, Indiana and Ohio. He had never been in the South.

Physical Examination. The patient was moderately well-nourished, but seemed acutely ill. His temperature was normal.

There was a generalized tenderness of the abdomen but no palpable tumor masses. The liver dulness was normal, the spleen and kidneys not palpable. Rectal examination was not regarded advisable at this time because of the discomfort to the patient. All reflexes were normal. The blood examination demonstrated the following: erythrocytes, 4,930,000; leukocytes, 16,650; hemoglobin, 95 per cent. The Widal test (1 to 50) was negative. The urine had a specific gravity of 1.020, an acid reaction, and no albumin, sugar, erythrocytes, leukocytes or casts were found. Blood was present in the stools (chemical tests). Cultures of the urine and stools contained no typhoid or dysentery bacilli.

Ulcerative colitis of unknown origin was diagnosed.

Treatment. The patient was given a high-protein diet. Kaolin, charcoal and calcium chlorid in buttermilk were prescribed, and belladonna ($\frac{1}{8}$ gr.) was given three times daily. Codein, veronal and powdered opium were prescribed at various times when necessary for sleep.

Course. From the first to the fourteenth day the patient's condition remained practically the same, excepting for a temperature of 102° F. on the fourth day, and again on the tenth. Thereafter, the temperature varied between 100° and 102° F., reaching 103° F. on the sixteenth day. The stools continued to be frequent, bloody and liquid. The diagnosis of amebic dysentery was considered, but repeated examinations of warm stools failed to disclose any amebæ. It was not thought advisable to make a proctoscopic examination as the pain incident would be out of proportion to the information obtained.

Cultures of the feces on the third day contained only *Bacillus coli*; on the sixth day, again *Bacillus coli*; on the eighth and tenth days, *Bacillus coli*; on the sixteenth day, *Bacillus proteus vulgaris* appeared. Faint traces of albumin in the urine appeared as the disease progressed.

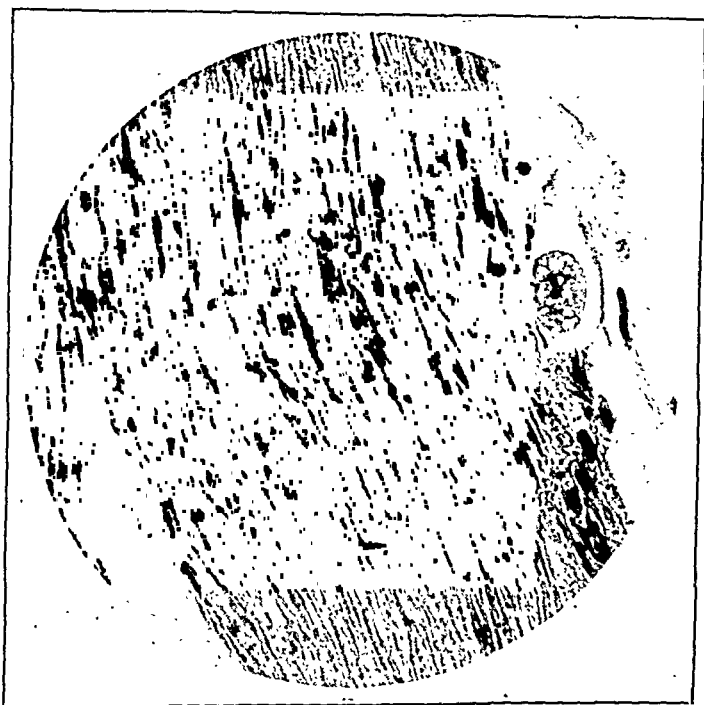
The blood examinations on successive days were:

Day.	Erythrocytes.	Leukocytes.	Hemoglobin, per cent.
1	4,930,000	16,650	95
5	3,980,000	70
8	3,925,000	79
13	3,880,000	13,950	70
15	26,250	

On the thirteenth day the patient complained of pain over the entire right side on palpation. Because of the symptoms of an acute peritonitis, an exploratory operation was decided on. Through a right rectus, muscle-splitting incision over the cecum, the abdomen was opened, and clear fluid was found in the peritoneal cavity. A stained slide preparation of this fluid contained many leukocytes, but no bacteria. Cultures prepared on blood agar and grown aëroically and anaëroically for forty-eight hours remained sterile.

While the surgeon was attempting to bring out the appendix for amputation, the extremely friable wall of the cecum was torn. No further surgery was attempted except to drain the cecum with a large rubber tube, and to close the abdomen loosely around the drainage tube. The patient's condition grew worse and death occurred three days after the operation.

Necropsy. By the usual postmortem examination of the trunk only, the essential changes demonstrated were present in the large bowel and rectum. The lining of the rectum was markedly reddened, especially below, and was covered with a thick yellow exudate. There was an ulcer 2 by 1.5 cm. just above the anus. It had an irregular red-brown base and was from 1 to 2 mm. in depth,



Microphotograph illustrating amebæ in the bowel wall near an abscess. $\times 560$.

with its edges undermined. There were about fifteen dark red polypi as large as 3 cm. in their greatest dimension attached to the lining of the rectum at different places. There were also multiple hemorrhages in the rectal mucosa. There was a gradual fading of the reddened mucosa toward the sigmoid, and 15 cm. above the anal orifice it was gray-pink. The polypoid masses here also were dark gray and brown. The lining of the colon throughout its length was dark gray and was covered with a thick exudate. The mucosa as well as that of the rectum was irregularly roughened; its normal markings were lost and it had a moth-eaten appearance. The wall of the entire large bowel was friable and tore easily. Scattered irregularly over the lining were polypoid masses, ray-brown in

color and up to 3 cm. in their greatest dimension. There was a marked reddening of the cecum and the first 17 cm. of the ascending colon. The ileocecal valve was moderately reddened and edematous and on the front wall was an irregular hole, 3.5 cm. long, with necrotic gangrenous edges. The appendix was 9 cm. long and 1.4 cm. in diameter. The lumen was patent throughout, with the lining markedly hyperemic. The distal 5 cm. was a hemorrhagic necrotic mass. There was no ulceration of the lining of the small bowel nor were there abscesses of the liver. The cultures of the heart's blood grown on blood agar aërobically and anaërobically remained sterile; of the exudate on the bowel lining and of the peritoneal exudate these were identified: (1) *Staphylococcus albus*, (2) *Streptococcus fecalis*, and (3) *Bacillus coli communior*. Histological preparations of the bowel lining demonstrated an extensive suppurative inflammation of the mucosa. There were deep undermined ulcers extending down to and into the muscularis. Careful search in specially stained preparations demonstrated amebæ of the size described for *Entamoeba histolytica*, and in their cytoplasm were engulfed red cells and other tissue fragments. In the granulation tissue spore forms were found.

CASE II.—E. H., a white man, aged forty-four years, entered St. Luke's Hospital, July 14, 1924, complaining of lassitude, a constant desire to defecate, watery stools with occasional mucus, pain over the lower abdomen and muscle soreness.

The onset occurred two months previously, while the patient was in Tennessee recuperating from an attack of pneumonia and a right empyema. Since that time the diarrhea had persisted, there being from five to fifteen watery stools a day, each accompanied by griping. The patient occasionally observed small amounts of bright red blood in the stools. He also had protruding painful hemorrhoids, and had been subject to attacks of muscle soreness and occasional joint pains. There had been no nausea, and no other complaints except a chilly feeling experienced early in the morning two weeks previous to admission. The patient felt well enough to be up and around.

Physical Examination. The patient was poorly nourished; he was not confined to his bed, but was weakened from the effects of the dysentery. Routine examination revealed nothing of importance except a tympanitic region over the transverse colon and the descending colon. The spleen and kidneys were not palpable. The blood count was: Erythrocytes, 4,650,000; leukocytes, 11,700, hemoglobin, 88 per cent.

A tentative diagnosis of amebic dysentery was made.

Treatment and Course. The patient was put on a fruit and vegetable-free diet. On the first day a rectal tube was inserted, and amebæ were isolated in the mucus recovered from the eye of

the tube. Emetin hydrochlorid (gr. 1 orally and gr. $\frac{1}{2}$ hypodermically) was started at once.

The temperature remained normal throughout. The patient's condition improved; the bloody stools ceased, but they still remained soft, and frequent. The patient was discharged on the twelfth day with instructions to continue with the emetin hydrochlorid under direction.

CASE III.—G. R., a white man, aged sixty-three years, entered St. Luke's Hospital for observation, August 12, 1924, complaining of watery diarrhea, urgency and slight tenesmus, loss of weight, weakness and lassitude. The onset occurred six weeks previously, while the patient was in Louisiana. Since then the diarrhea had been continuous, there having been six bowel movements a day. On August 7, 8 and 9 he received three intramuscular injections of emetin hydrochlorid, but did not notice any change in his condition.

Physical Examination. The patient was well-developed, and apparently not in any pain or discomfort. Examination was negative, except for a slight tenderness on deep palpation over the descending colon. The blood count was: Erythrocytes, 4,165,000; leukocytes, 14,200, and hemoglobin, 90 per cent.

Microscopical examination of the mucus and blood in the stool demonstrated the presence of *Entamoeba histolytica* in considerable numbers and actively motile. The urine contained a faint trace of albumin, occasional epithelial cells and many leukocytes.

Amoebic dysentery was diagnosed.

Treatment and Course. The patient received 1 gr. of emetin hydrochlorid intramuscularly, and was given instructions to continue this at home until 8 gr. had been taken in eight days. Then if the diarrhea subsided, treatment was to be suspended for a month and four more injections given. After another month's interval, this was to be repeated.

CASE IV.—G. S., a white man, aged eighty years, entered St. Luke's Hospital, July 24, 1924, complaining of diarrhea which began three weeks before while the patient was in Texas. There was a gradual increase in the frequency and watery consistency of the stools. At the most, they numbered six during a twenty-four-hour period. No blood was observed in the stools. There had been no griping, and the patient had been fairly comfortable. He had been treated by dietary methods (milk-toast diet). He did not know the source of the drinking water he obtained in Texas.

Physical Examination. The patient was fairly well-nourished. The ascending, transverse and descending colon were tympanitic. No abdominal masses were felt. The blood count was: Erythrocytes, 4,365,000, leukocytes, 8800, and hemoglobin, 89 per cent.

Treatment and Course. A proctoscope was inserted and mucous material was collected, in which motile amebæ containing ingested red cells were found. The patient was placed on a fruit and vegetable-free diet, and was given emetin hydrochlorid (gr. 1). Eleven days after admission no amebæ were found and the patient was discharged.

CASE V.—H. H., a white man, aged thirty-one years, complained of having cramps in the abdomen, diarrhea, bloody stools and loss of weight. This trouble had been persistent for two weeks, except when he took a morphin preparation which a physician had given him. The patient had about ten bowel movements a day; the stools contained bright red blood and mucus. He lost 14 pounds in weight and had become extremely nervous. He had lately been South as far as St. Louis.

Treatment and Course. Examination of the feces demonstrated amebæ. Emetin hydrochlorid was administered in a series of eight doses, starting with $\frac{1}{4}$ gr. and increasing to 1 gr. Four days later the bowel movements were quite regular and there was no tenesmus. During the following three days the patient had only one bowel movement a day. He was instructed to return after two months for another series of five injections.

CASE VI.—W. C., a white man, aged seventy-seven years, entered St. Luke's Hospital, September 24, 1924, complaining of diarrhea. The patient had been well and had carried on his work until about three weeks prior to admission. At this time he complained of some indigestion and constipation; he went on a diet and was apparently relieved for a few days. A week later he began to feel much worse with a pain in the left lower quadrant. He called an osteopath who gave him treatments. One week before entering the hospital he complained of severe pain and swelling of the big toe of the left foot—a gouty inflammation which he had had before. He was given colchicin for two days, which precipitated a diarrhea. For two days before entering the hospital he had blood in the stools.

Six years before the patient's present illness, he had an attack of dysentery the cause of which was not determined.

Physical Examination. The abdomen was somewhat distended and there was a definite resistant mass in the left lower quadrant. There was a non-movable dulness on percussion in the left flank. There was a leukocytosis of 18,000 and a temperature of 100° to 102° F. On account of these symptoms a diagnosis was made of a localized peritonitis due to some inflammatory condition in the region of the sigmoid flexure and it was thought that an ulcerative condition of the bowel was responsible for the blood. The stool contained mucus and blood, but no dysentery bacilli. The advisability of a laparotomy was discussed with a surgeon but was not deemed advisable.

For three days the patient gradually grew weaker, tympanites increased, and death occurred on the fourth day.

Necropsy. The essential changes demonstrated by the post-mortem examination of the trunk only were limited to the large bowel and rectum, excepting a slight generalized acute serofibrinous peritonitis. In the lining of the colon and rectum there were multiple, closely-set abscesses up to 2 cm. in their greatest surface dimension. They contained a thick yellow exudate. In the rectum there were undermined ulcers of about the same size. There was a marked edema of the mucosa lining the large bowel and the rectum. Examination of the exudate on a warm stage demonstrated large numbers of *Entamoeba dysenteriae*.

Discussion. The confusion and bewilderment attendant on the diagnosis of acute ulcerative colitis has been due, in part, to the great variety of entities that have been included under the title of this disease. Practically speaking, the present discussion is limited to those cases of acute ulcerative colitis characterized by a sudden onset and speedy termination in death, without the cause having been determined soon enough to treat successfully. One writer speaks of it as being "a disease of the postmortem table." Hitherto it has been unfortunate that in many of these cases we have not been able to diagnose the disturbance during the lifetime of the patients, and hence our studies have been confined to the post-mortem aspects of the disease; consequently, only the more severe features could be studied.

There are many different acute forms of ulcerative colitis: it often appears in infants, or accompanies chronic (infective) endocarditis and chronic dysentery, and occurs in terminal conditions in certain chronic diseases, especially nephritis. Lastly, there is the innominate form of ulcerative colitis, and it is this form with which this paper deals.

In order to avoid misunderstanding as to the type of colitis under consideration, we may list the recognized criteria of true acute ulcerative colitis of unknown origin as follows: (1) Diarrhea, more or less persistent, with stools frequent in number and possessing dysenteric characteristics; (2) the presence of blood in the stools at some time or another, with or without mucus, sloughs and pus; (3) abdominal pain, general or local, with or without rectal pain; (4) some degree of fever; (5) loss of flesh, and (6) duration of the disease for longer than one week.

Acute ulcerative colitis, apart from the form known as tropical dysentery, has been considered so fatal a disease that some writers think that there is no cure for it, and that cases diagnosed as such, which have resulted in recovery, could not have been true forms of acute ulcerative colitis. Our experience would appear to disprove this. Acute ulcerative colitis of unknown origin is so rare and so fatal that men have tacked on the terms "idiopathic" and "innomi-

nate" to its name, the literature has been so cluttered up with the many different types of dysenteries, and experimental evidence has been so diffuse that we wonder whether there is such a thing as "acute ulcerative colitis of unknown origin." Of course, we are aware of the confusion that exists between acute ulcerative colitis and tropical dysentery—a confusion which is still far from being ended—and certainly we would not go so far as to say that all cases of acute ulcerative colitis are examples of tropical dysentery—still, when we find two cases that fit, in every detail, into the clinical picture of acute ulcerative colitis, and which are found to be amebic in origin, we question whether many of the cases reported in the literature as being acute ulcerative colitis of unknown origin would not have been found to be cases of amebic dysentery if proper time and study to the microscopical examination had been given by competent laboratory workers.

There may be some difficulty in demonstrating the organisms in the chronic state especially when considerable portions of the bowel lining have been destroyed. Repeated examinations should be made with these. The amount of mucosa regenerating after an extensive suppurative inflammation may not permit complete healing and in these patients, even after emetin treatment, a chronic suppurative inflammation will persist.

We have reported these other cases of amebic dysentery to show that this disease is not so rare as it has been considered in the literature bearing upon this type of colitis. Another reason, perhaps, why cases of amebic dysentery have not been reported is that there is nothing unusual about them, and the etiology and histology have been so well worked out that the majority of men thought them not unusual enough to report.

In combating desperate cases where the diarrhea is distressing, the practitioner is armed with a long list of drugs, such as the following: Tannigen, bismuth subnitrate, bismuth salicylate, flushings of 1 per cent tannin or 1 to 1000 salicylic acid; aromatic sulphuric acid, antiseptic betanaphthol and phenol salicylate, thin starch to which from 20 to 30 drops of laudanum has been added; nitrate of silver and sulphate of copper; acetate of lead, and alterative doses of castor oil, $\frac{1}{2}$ dram after meals. He uses these singly or in combination, finally coming to the conclusion that he is powerless to control the diarrhea, because he has been unable to find the right drug or the right combination of drugs. The literature is full of case reports listing the usual variety of remedies used to check the diarrhea, and which inevitably end with the worn-out statement that they have "failed to check it."

In trying our various drugs which have been handed down for years and years (and each few years adds a new one to the list), we have discovered that unfortunately this type of dysentery is not influenced by any of them. From our experience, though, it would

seem that the empirical use of emetin might be effective in some of the cases which have baffled the diagnostician. Incidentally, at this point we should like to warn particularly against an opinion that is very prevalent, namely, that when moderate doses of kaolin fail to combat this diarrhea, massive doses of 4 or 5 ounces a day should be given. It is obvious that large doses of barium or kaolin may cause a perforation of the intestine.

We have all felt that since the advent of the proctoscope and the roentgen-ray, the diagnosis of the dysenteries would be rendered relatively simple. It is unfortunate, however, that we cannot look to either of these instruments of precision as an aid in diagnosing these cases. In the majority of cases we are forced to exclude the use of both the roentgen-ray and the proctoscope, because of the danger of rupturing the intestine. It is the rapidity with which the colon becomes necrotic that makes both the barium meal and the proctoscope such dangerous procedures to use, as borne out by the fact that in one case an operation was performed twenty-three days after the appearance of the first symptoms, and the colon could not be picked up without its being ruptured. In the case of desperately sick patients we are often not justified in submitting them to the routine of the roentgen ray or proctoscopic examination. For instance, there was no period in the course of the disease in Case I which we could have chosen as the proper time for such an examination, and it presumably was just as well, for we would undoubtedly have caused a perforation at almost any time after the patient came under our observation.

With possession of these facts, how amazed one is to read a recent article in a report of 250 cases, in which the author makes this statement: "The failure to detect early the large number of diseased conditions in the terminal colon results from a neglect to examine all patients with the sigmoidoscope, however slight the symptoms." This is a typical modern statement, and gives voice to an unfortunate modern conception of making diagnoses. There is no possible way to detect from the condition of the patient the condition of the colon, and therefore we should be alert to the accidents that could happen with such instruments as the proctoscope—accidents which often are never discovered unless a necropsy is performed. It is rather surprising to find that, with the great number of cases reported in this article, there seems to be no contraindication to this drastic procedure. We could leave it to the imagination to picture what would happen to a colon following the insertion of a proctoscope or the passing of a rubber tube to the sigmoid; or irrigation (silver nitrate, argyrol), when, as in Case I, in two weeks from the onset of the disease the colon was found at operation to have the consistency of wet blotting paper.

Operations in this type of case are usually delayed and performed only as a last resort. We are so unaccustomed to thinking that the

"last resort" of a dysentery occurs within such a short time as it did in Case I that it would be impossible to think that an ileostomy could have helped the patient unless it had been performed two weeks after the onset. The lack of experience of surgeons and the lack of early guiding symptoms cause us to neglect operating in these cases early enough to be beneficial.

Thanks are due to Dr. Joseph M. Miller for the privilege of reporting 2 cases of amebic dysentery, to Dr. Joseph Capps for the privilege of reporting 1 case, and to Dr. Eugene Talbot for another case.

Summary. 1. The possibility of amebic infection in patients with a chronic ulcerative colitis should be considered, and there should be a search for amebæ before a diagnosis of idiopathic ulcerative colitis is made.

2. The usual medication including large doses of kaolin, bismuth, and other astringents is not indicated where the infection is definitely amebic.

3. Because of the extensive ulceration and friability of the bowel wall with amebic dysentery, the proctoscope should be used with extreme caution.

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DUODENAL DIVERTICULOSIS, WITH REPORT OF A CASE SEEN ROENTGENOLOGICALLY.

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Up to the year 1912 duodenal diverticulosis was actually unknown clinically. In reviewing the literature on the subject Case¹ found that 82 cases of duodenal diverticula had been reported from 1761 to 1911.

In 1915 Case¹ himself reported a series of 7 cases he found in routine roentgenologic examination of the gastrointestinal tract; later, in 1920,² he again reported on a sum total of 85 cases of diverticula of the small intestine in 6847 complete barium-meal studies.

Other authors, such as Akerlund,³ Cullen,⁴ Cole and Roberts,⁵ Holzweissig⁶ and many more have since contributed to our knowledge of this entity and impressed the profession with its greater frequency as well as the dangers that may at times accompany this condition. Constant perfection in technic is no doubt responsible for the ever increasing number of cases detected during roentgen-ray examination of the gastrointestinal tract.

Although this subject has been so fully and thoroughly considered by various authors, yet it would not seem amiss to add the following case to the list of those already reported, for these reasons: (a) Relative infrequency of duodenal diverticulosis; (b) multiple diverticula in the case illustrated; (c) infrequency of the location of one diverticulum (D^2); (d) size of the diverticular shadows.

It is interesting to note that this patient gave no symptoms that were directly attributable to the diverticulosis.

Case Report. Mrs. M. N., aged sixty-five years, housewife, complained of diarrhea of four months' duration, manifesting itself in five to six bowel movements a day, this being associated with abdominal distention and at times cramps about two hours after the ingestion of food. Her family history as well as the past history is essentially negative. The present complaint dates back to four months ago when she was taken ill with what she called a "nervous breakdown." This condition lasted for a period of four weeks. At present in spite of her general condition being much improved the gastrointestinal symptoms are still persisting. There is no loss of weight, appetite is good and there is no abdominal pain.

Physical examination reveals nothing of importance, with the exception of considerable abdominal distention and diffuse tenderness throughout the abdomen.

Laboratory findings: The urine examination is negative. Examination of gastric contents showed the total amount aspirated one hour after an Ewald meal to be 35 cc, with a total acidity of 20 degrees; free hydrochloric acid, 10 degrees; no occult blood; microscopical examination is negative. Stool examination is negative.

Roentgenographic examination of the gastrointestinal tract reveals a marked gastrointestinal hypermotility which is not referable to any visible organic lesion; also the duodenal diverticula as shown in the accompanying illustrations are visualized.

Attributing this hypermotility to a gastric hypochlorhydria and treating her on the basis of this presumption, I succeeded in checking the diarrhea quite promptly.

At present the patient's condition is good. The diverticula found have obviously no bearing on the above described symptomatology, and she refuses to consent to an operation.

Discussion. As to the etiology of this anomaly, a number of opinions have been offered by various authors. Some of these cases are no doubt congenital in origin, since they have been found in

infants. Nevertheless, age seems to play an important role as an etiological factor, a great majority of cases being found in the

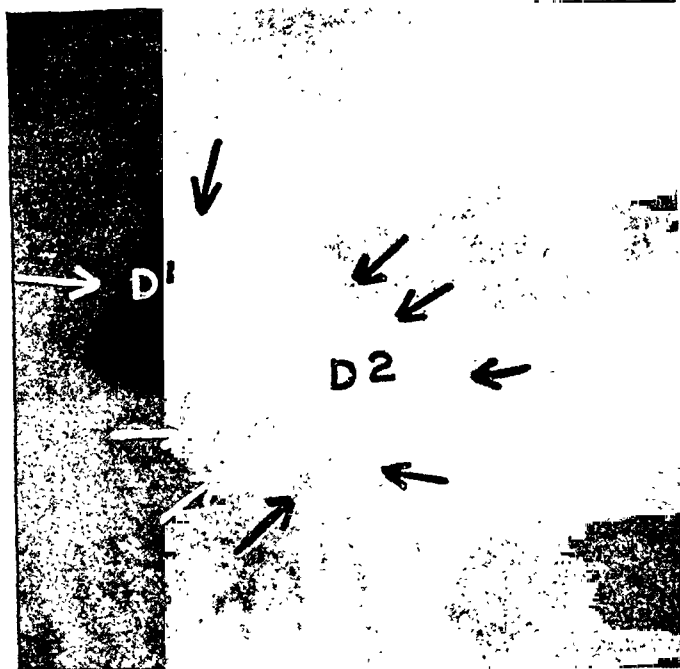


FIG. 1.—Roentgenogram showing duodenal diverticula. D^1 is a diverticulum in the second portion and D^2 a diverticulum in the transverse portion of the duodenum.

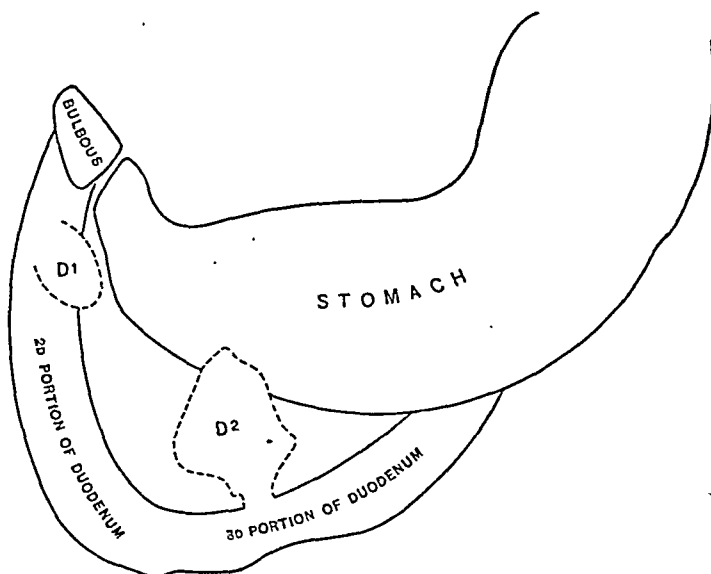


FIG. 2.—A diagrammatic representation of Fig. 1; D^1 and D^2 representing the diverticula.

seventh and eighth decades of life. This can perhaps be attributed to a loss of elasticity in certain parts of the intestinal wall, which

may accompany old age; or may be associated with an increased intrainestinal pressure. Such a condition may be the result of a chronic ileal or colonic stasis or perhaps repeated localized intestinal spasms.

Holzweissig⁶ in 1921 contributed a very thorough and lengthy discussion concerning the etiology of duodenal diverticulosis, wherein he attempted to prove with the aid of stained preparations of sections of the intestinal tract, that the piercing of the intestinal musculature by the bloodvessels create loci minoris resistentiæ, permitting the mucosa of the intestine to form herniæ through the musculature.

The piercing of the second portion of the duodenum by the common bile duct and Wirsung's duct may operate in the same manner in the production of a diverticulum. These diverticula are spoken of by the French authors as the "peri-Vateran" diverticula, and these cases constitute a high percentage of this anomaly.

Other factors which may enter into the etiology of these diverticula are chronic peptic ulcers, chronic cholecystitis with cholecystoduodenal adhesions, cholelithiasis and recurrent attacks of duodenitis.

These diverticula are usually single; sometimes, however, as many as three and four may be found, and these are at times associated with a colonic diverticulosis. They vary in size from a pea to that of a small pear. In Case's series the average size of the shadow of the barium filled diverticulum was 2.8 cm. In the case reported here the greatest diameter of the diverticular shadow, as seen on the original film measures 6 cm. The most usual sites for these duodenal pouches, as they are found in their order of frequency, are: In the second portion of the duodenum 57.5 per cent; in the third portion and the duodenojejunal junction, 22.5 per cent; in the first portion of the duodenum, 20 per cent.

Upon examination these diverticula present an arrangement of structures comparable to that of a true aneurysm in which the intima has herniated through the outer coats of the vessel. They are composed of a mucosa lined with a smooth epithelium, which may show, as a result of distention thinned out areas. The glands of Lieberkühn as well as bits of pancreatic tissue are frequently found in the mucosa of the diverticulum. The muscularis coat, as a rule, is absent except for a few fibers scattered around the opening leading into the intestinal lumen.

About the symptomatology nothing definite can be said, as this condition does not present a definite symptom complex whereby a positive diagnosis may be established. Most of these cases are detected during the course of routine roentgen-ray examination of the alimentary tract. In some of these, however, the diverticulum may cause retention of large quantities of food, resulting in periodic intestinal attacks of a toxic nature, with or without pain. At

times these attacks may simulate those of a chronic or even acute ileus. Perforation of the sac with a fatal outcome has also been reported in the literature.

Summary. A case of duodenal diverticulosis, showing two diverticula in the second and third portions of the duodenum respectively, with roentgenographic findings, is reported.

The infrequency of this condition is pointed out, Case reporting characteristic evidence of duodenal diverticulosis in about 1.2 per cent of 6847 cases radiographed.

The most usual sites of these diverticula in their order of frequency are mentioned, namely: In the second portion of the duodenum, 57.5 per cent; in the third portion and duodenojejunal junction, 22.5 per cent, and in the first portion of the duodenum 20 per cent.

Various theories as to the etiology of this anomaly are quoted; the actual factors operative in its production are no doubt obscure in many cases.

The great majority of cases do not at any time present any definite symptomatology; they are usually discovered in the course of a routine roentgen-ray examination of the alimentary tract.

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THREE CASES OF TULAREMIA, ONE RESEMBLING SPOROTRICHOSIS.

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THE occurrence of proven cases of tularemia in man has been reported from so many different parts of the country that its widespread nature is manifest. Details of its history and etiology are here omitted, as they are described elsewhere.

The three following cases were found in game dressers in the Huntington market:

Case Reports. CASE I.—C. W., a married white man, aged thirty-one years, was referred to the writer by Dr. I. W. Mayberry, because of the continued recurrence of abscesses on the left arm

and forearm. His present illness began on November 20, 1924, with a dusky red spot on the proximal phalanx of the middle finger of the left hand. Previous to this time he had been so well that he had never consulted a physician.

History. The beginning of the open season for rabbits was on November 15, on which date he first dressed one, and it was five days later that the sore appeared. The finger became enlarged and tender, as did the two adjacent ones; the temperature went



Case I.—This shows the initial finger lesion, the draining axillary incision and the purplish-red scars. Over the biceps there is an early, deep-seated, indurated nodule.

to 103°, at which it continued for seven days, accompanied by delirium. The primary sore broke, and much pus was evacuated. He was confined to his bed for eighteen days, and was treated for "flu pneumonia." At the end of this period he noticed the appearance of an enlarged tender gland in the axilla of the affected limb, and also the formation of a scum over both eyes, followed by small yellow bumps on the conjunctivæ. The axillary gland was lanced, a large amount of pus being obtained. The conjunctivitis dis-

appeared in time, but small lumps continued to appear at intervals on the left arm and forearm, only one appearing elsewhere, this being over the twelfth thoracic spine. The distribution was quite irregular. They appeared first as deep, tender, indurated nodules, the overlying skin being freely movable and not discolored. The nodules gradually enlarged to a diameter of 0.5 to 2 cm., and in five to seven days fluctuation developed, with sometimes a purplish discoloration of the overlying skin. Upon deep incision, a thick, light green material was obtained. The pain was thereby relieved, and the wound always healed well, never to give any further trouble. He continued to run a slight fever at intervals until March 20, after which the temperature has remained normal.

Physical Examination. March 20 (condensed). The patient is thin, of fair muscular development and anemic. His weight is 150 pounds, the normal being 170; he is gaining at present. The skin has a normal texture and moisture over the body. Over the left arm and forearm the purplish red scars of many abscesses are seen and one deep, indurated nodule over the center of the biceps. The first abscess, which appeared in the axilla, continues to drain slightly at intervals. The skin over the left hand has a peculiar purplish-red color, and the extremity is colder than the other one. The cervical, axillary, epitrochlear and inguinal nodes are not enlarged. The tonsils, teeth and sinuses show no abnormalities. The heart, lungs and the abdominal viscera are normal. The temperature is 99.3°; the pulse, 100; the blood pressure: systolic, 118; diastolic, 70.

Laboratory Examinations. The urine shows a distinct trace of albumin; no sugar. There are four small hyalin casts per low-power field. Blood: White blood cells, 12,900; polymorphonuclears, 68 per cent; lymphocytes, 27 per cent; mononuclears, 3 per cent; eosinophils, 2 per cent; red blood cells, 4,208,000; hemoglobin, 68 per cent Sahli; color index 0.8, red cells are normal in shape and staining properties. Serological: The Wassermann test is negative; the agglutination test with bacterium tularensis, done at the Hygienic Laboratory in Washington by Dr. Edward Francis, was positive in all dilutions from 1 to 10 to 1 to 640 and negative in higher dilutions. Bacteriological: Microscopical examination of the green discharge from the lesions showed necrotic material containing no microorganisms. Repeated cultures on glucose agar, glucose broth and Sabouraud's maltose agar were negative. A guinea pig inoculated with the material remained well.

Roentgen-ray Examination. Roentgen-ray examination of the bones of the left arm and forearm was made because of the similarity to sporotrichosis, which exists in this region. No bony cysts were found, nor was there bone involvement of any kind.

Treatment. This was symptomatic until February 20, when first seen by the writer, when a diagnosis of sporotrichosis was made.

The patient was given the iodides, after which only one more nodule developed, and the temperature became permanently normal in ten days.

CASE II.—M. B., a white married man, aged twenty-six years, was a friend and co-worker of the first patient. Prior to the present illness he had been very healthy.

During November, 1923, the open season for rabbits he cut his left hand between the thumb and index finger while dressing one. The wound became very sore, and the infection traveled to the axilla. The temperature went to 103.5° , and he was confined to his bed for three weeks, being treated for pneumonia. The axillary glands became larger and more painful, and were lanced, a large amount of pus being obtained. He was kept from his work for four months, and even after that time was weak, improvement taking place very gradually. These two lesions were the only skin manifestations. He had no conjunctivitis. His normal weight was 145 pounds, but during his illness he fell to 120 pounds. At present he has regained his lost weight. The patient was not seen until after his complete recovery, hence the omission of details.

The blood serum was sent to Dr. Francis for an agglutination test with *Bacterium tularensis*. He reported a positive in all dilutions from 1 to 10 to 1 to 40, but negative in higher dilutions. Dr. Francis states that he has never found a human serum other than tularemia to agglutinate in this dilution.

CASE III.—G. K., a bachelor, aged sixty-two years, was employed in the same capacity, and in the same place, as the two patients above reported. On December 18, 1923, he was taken ill with fever, and a sore on his right hand between the middle and the ring fingers. An abscess formed, which broke on Christmas morning, discharging a green pus. It continued to drain for six weeks, and he was kept from work until April. Even at that time he felt weak, and was but slowly regaining his lost weight. He recalls no axillary soreness. At present there is no cervical or axillary enlargement. His affected hand is partly drawn and cold. Some disability still exists, due to the pull of scar tissue. There was no skin manifestation other than the abscess mentioned, and no conjunctivitis.

Serological findings: On April 15, 1925, an agglutination test for tularemia was done by Dr. Francis, who reported it positive in dilutions of 1 to 20 and 1 to 40, but not in higher dilutions. He states that that is the titer of his own serum five and a half years after his attack. The blood Wassermann test on this same date was negative.

Comment. In the first case the close resemblance to sporotrichosis is of special interest. The method of onset, the positive

agglutination tests with *Bacterium tularensis*, the persistently negative cultures, the negative guinea-pig inoculation and the absence of bone cysts serve to prove that it was not a yeast infection. The occurrence of a conjunctivitis, probably tularemic, is also noted. The improvement after iodid administration probably was coincident with the improvement naturally taking place.

The other cases correspond closely to ones described elsewhere, and are reported because of the comparative newness of the disease.

Conclusions. Three cases proven to be tularemia are reported, all of which were contracted from handling infected rabbits. One case resembled sporotrichosis, and had a complicating tularemic conjunctivitis. The others ran a course similar to the average described case. No treatment of proven merit was employed.

MALIGNANT TUMORS OF THE THYROID: AN ANALYSIS OF SEVEN CASES WITH A STUDY OF THE STRUCTURE AND FUNCTION OF THE METASTASES.

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MALIGNANT disease of the thyroid is of especial interest to the clinical pathologist, because the peculiar function of the tissue in which it grows affords a criterion for the study of the physiology of the malignant tissue cell, which is not possible in malignancy elsewhere in the body. The disease is comparatively rare. L. B. Wilson¹ has collected from the records of the Mayo Clinic and from the literature 972 cases of which number about 80 per cent are of the carcinomatous type. In the incidence of malignant tumors in general, the disease plays only a small part. Among 40 cases of sarcoma and 624 cases of carcinoma admitted to Montefiore Hospital from July 1, 1914 to July 1, 1924, there were only 8 cases (1.2 per cent) of malignancy of the thyroid—1 sarcoma and 7 carcinomata. Of these, 1 case has been reported by Skversky² and will not be included in this series.

It is the opinion of most writers that malignant disease of the thyroid seldom, if ever, occurs primarily in a healthy gland. It is believed to be preceded always by pathological changes, most commonly of the adenomatous type, which Balfour³ looks upon as the premalignant condition of the thyroid. Speese and Brown found that benign tumors preceded the development of malignancy in practically every one of their cases of cancer of the thyroid. This

has not been our experience. Only one of our cases gave a history of a swelling in the thyroid region previous to the onset of clinical symptoms of malignancy.

The incidence of malignant disease of the thyroid is greatest in those regions where goiter is most frequent. Limacher⁴ in Berne, where goiter is very common, in 7461 routine autopsies, found 82 cases (1.09 per cent) of malignant disease of the thyroid, while Huguenin⁵ in Guenf, where the incidence of goiter is not so great, in an almost similar number of autopsies (7356), found only 25 cases (0.35 per cent) with malignancy of the thyroid. Its greater incidence in people with a definite evidence of goiter, (1.9 per cent in a series of 14,456 cases in the Mayo Clinic), as compared to its occurrence among the general population that come to routine autopsy (0.0027 per cent), points in the same direction.

The age incidence of malignant disease of the thyroid is about the same as that of malignancy elsewhere in the body, except that sarcoma does not here show its characteristic predilection for the earlier age groups. The greatest incidence is in the fourth and fifth decades (6 of our 7 cases), but about 20 per cent of all cases occur under forty years.

The disease is more common among females, (7 to 3 in the Mayo Clinic cases; 5 to 3 in our series) in whom goiterous enlargements of all kind are also more frequent.

Pathology. Sarcomata and carcinomata are found. The latter were divided by Langhans into seven types. The most common, probably, is the simple carcinoma composed of solid strands or masses of atypical cells showing no alveolar differentiation. Metastases showing well marked alveolar formation were at one time looked upon as disseminated nodules of benign thyroid tissue from a "metastasizing colloid goiter" or from a proliferating adenoma. It has since been definitely shown that these are true carcinomatous metastases, occasionally found together with the solid type and due often to a small, even microscopic primary carcinoma of the thyroid. Papillary carcinomata, either solid or cystic in type, are occasionally found. Squamous-cell carcinomata are rare. They are derived from the remnants of the thyroglossal duct. The "postbranchial goiters" are so named from their reputed derivation from the postbranchial body. Parastruma is the name applied to masses of large, clear cells resembling somewhat those of the normal parathyroid.

The sarcomata are of various cellular types. Round cell, spindle cell, mixed cell and occasionally giant cell varieties have been described. We have seen a lymphosarcoma of the thyroid, but there was nothing to indicate that this was its primary seat of origin. The structure of these varies from that of a typical fibrosarcoma to an alveolar arrangement strongly resembling the alveolar types of carcinoma. The histological as well as the clinical

differentiation between sarcoma and carcinoma is not as well marked in the thyroid as it is in other organs. Cases have been described showing both a sarcomatous and a carcinomatous structure in the same tumor. So poorly marked is the line of differentiation between these two types of malignancy that Ewing⁶ is unwilling to believe that the so-called sarcomata of the thyroid are of true mesoblastic origin. He regards them rather as essentially ectoblastic tumors with a hyperplastic stroma.

Symptoms and Clinical Course. The disease usually begins with the appearance of a swelling at the base of the neck or with the sudden onset of growth in a long-standing goiter. The local condition may be of various degrees of prominence leading to the formation of a tumor of various size up to that of child's head and forming the initial and out-standing symptom of the disease by the resulting compressive phenomena. Occasionally, however, the local symptoms are a negligible factor; there may be absolutely no visible or palpable lesion in the thyroid and the whole picture may be dominated by the metastatic phenomena. In a case from this hospital reported by Skversky,² the patient, who complained of pains in the legs, had been treated for neurasthenia and for osteitis of the lumbosacral region. Autopsy showed metastases to the spine from a very small carcinoma of the thyroid, which, during life, had attracted no suspicion whatever.

Metastases may or may not take place. When present they may occur at any time during the course of the disease and the dissemination may be by the lymphatics, by the blood stream or by both. The most frequent site of lodgment is the lungs, next the osseous tissue, then less commonly the liver, kidneys and pleura. Cancer of the thyroid stands out prominently among carcinomata elsewhere in the body as being the most prone, next to cancer of the breast and possibly of the prostate, to metastasize to the skeleton. The skull, inferior maxilla, sternum, the long bones and the pelvis are invaded in the order of frequency mentioned. The skeletal metastases are of the osteoclastic type, there being usually no sign of any attempt at new bone formation. Occasionally, however, especially in the sarcomata, osteoplasia does take place. We have seen at least one case where bony union has taken place after a pathological fracture induced by a metastasis of a sarcoma of the thyroid.

The disease usually runs its course in from two to four years. Acute fulminating types have been described with inflammatory symptoms causing death in a few weeks from general dissemination. Cases of the adenomatous type are inclined to have a more prolonged course. Sarcomata are said to be rapidly fatal, yet one of our cases (Case V) with a metastasis to a rib is alive and engaged at fairly arduous work three and a half years after the clinical onset of the disease.

Case Reports. The following cases were treated at Montefiore Hospital during the six years from 1918 to 1924. The reports of 3 of these are taken from the records; the remaining 4 were seen personally.

CASE I.—B. K. (1782), a man aged forty years, was admitted on June 9, 1918, with a history of severe, cutting, cramp-like pains in the left groin radiating into the left testicle and upward into the left lumbar region, commencing in July, 1917. This was followed by severe pain in the entire back and in the right hip and by the appearance of many small swellings over the ribs and behind the ears. There was a loss of 50 pounds in weight. Physical examination disclosed a very hard, non-tender tumor the size of a pigeon's egg adherent to the deep fascia of the front of the neck and to the laryngeal cartilage. Scattered all over the chest were many very painful, tender, oval masses $\frac{1}{2}$ to 1 inch in diameter, firmly attached to the underlying tissue but not to the skin. Roentgen-ray examination showed irregular bone destruction all over the left side of the pelvis and left femur, in the bodies of the vertebræ and in the ribs, with multiple pathological fractures in the latter. Clinical course was marked by the appearance of new masses over the ribs until the patient's death on September 9, 1918. No autopsy was obtained but the clinical diagnosis seemed definite.

CASE II.—D. K. (4233), a man, aged fifty-one years, was admitted on May 11, 1921, giving a history of having had a hard tumor on the right side of the neck gradually enlarging until four years ago when it had reached the size of a small orange, causing difficulty in breathing and swallowing. Operation at Mount Sinai Hospital on September 15, 1920, revealed a tumor of the thyroid which, on examination by Dr. Geist, proved to be a "medullary carcinoma." One month after operation patient began to have pain in the upper chest and in the left elbow with loss of function in the latter. There was great weakness and loss of 35 pounds in weight. Examination showed the entire region of the thyroid, both sterno-clavicular articulations and the manubrium sterni to be dominated by a massive, hard, nodular tumor attached at its base. There was marked increase in submanubrial dulness. There was a tense swelling of the left forearm with ankylosis of the elbow. Roentgen-ray showed an intrathoracic mass continuous with the thyroid tumor and extensive destruction of the lower end of the humerus. Patient left the hospital of his own accord on June 25, 1921.

CASE III.—L. Y. (9616), male, aged forty-eight years, was admitted on May 9, 1922, with a history of the appearance of two small nodules on the left side of the neck eighteen months previously. These had rapidly increased in size and were removed at Beth

David Hospital. Shortly after the operation the patient developed shooting pains in both legs. Examination showed the sternal end of the right clavicle to be thickened, forming a bony tumor the size of a hen's egg. There was a soft movable mass over the left apex. Roentgen-rays showed destruction throughout the right clavicle, humerus, ilium and femur. Course was gradually downward until patient's death on February 17, 1923. No autopsy was obtained.

CASE IV.—J. B. (11,153), female, aged seventy-two years, was admitted May 7, 1923. First symptom was the onset of snoring during sleep three years before admission, followed by slight dyspnea and the appearance of a small indurated swelling in the thyroid region. Tracheotomy was done at the Memorial Hospital to relieve dyspnea and at the same time a biopsy was done which showed a papillary adenocarcinoma of the thyroid. Examination showed a moderately cachectic woman with a hard mass about 3 cm. by 3 cm. in size in the thyroid region. Roentgen-ray studies revealed no metastases. Clinical course was marked by progressive increase in the size of the mass, in the dysphagia and the cachexia until the patient's death on March 6, 1924.

CASE V.—G. B., female, aged fifty-five years, first seen at the Radium Clinic on May 2, 1923, gave a history of having noticed the appearance of a nodule the size of a pea on the right side of the neck in February, 1922. This had gradually increased in size. She had been given two radium applications at one month's intervals followed by operation at Mount Sinai Hospital by Dr. A. V. Moschkowitz, at which an encapsulated mass involving the right lobe and isthmus was removed and found on microscopical examination to be a papillary adenocarcinoma of the thyroid. Her only complaint when first seen was a slight difficulty in swallowing. Examination showed a diffusely indurated area in the tissue between the skin and the larynx and a slight increase in retromanubrial dulness, otherwise entirely negative. Roentgen-ray examination showed a substernal thyroid. No clinical or roentgenological evidence of local recurrence or of metastases could be found on repeated examination. Patient has been given surface applications of radium over the thyroid region and prophylactic roentgen-ray treatments over the chest and pelvis and is now apparently well, with no sign of any recurrence two years after the operation and three years after the clinical onset of the disease.

CASE VI.—H. S., male, aged forty-four years, was first seen at the Radium Clinic on July 1, 1923. About two years previously patient had noticed in the thyroid region a small swelling the size of a pebble which had since increased in size. About eight months previous to date first seen, patient after slight exertion had felt

what he thought was a rib cracking on the right side of the chest and had considerable pain on breathing thereafter. Biopsy specimen from the rib done at Mount Sinai Hospital was examined by Dr. Mandelbaum and found to be a mixed-cell sarcoma with round and spindle cell elements. Examination on admission showed an asymmetrical enlargement of the anterior surface of the neck forming a mass 7 cm. by 9 cm. by 3 cm. which moved on deglutition, was not tender and did not interfere with breathing or swallowing. Roentgen-ray examination showed a large mass, evidently the thyroid, pushing the trachea to the right and partially compressing it. There was a fusiform mass over the middle third of the eighth rib on the right side with considerable bone absorption in this region. Repeated pictures of this mass showed a slight but definite decrease in size and increase in density. Patient is now apparently well and engaged at fairly arduous manual labor three and a half years after the clinical onset of the disease. Treatment given is the same as in the previous case.

CASE VII.—This case is reported in more detail because of its unusual clinical interest and because it was made the basis of a study which may perhaps throw some light on the pathology of this type of cancer.

P. S. (11,855), female, aged fifty-two years, was admitted on June 21, 1924. Her illness began in the summer of 1922 with the sensation of a lump in the throat accompanied by a difficulty in swallowing. In October, 1923, the patient began to have burning pains in the left side of the chest radiating down the left arm and several weeks later noticed a small, hard, painless lump in the right breast just above the nipple. About December, the patient began to have aching pains down the back of both legs and about the same time it was noticed that her voice was becoming husky. By March, 1924, the mass in the right breast has grown considerably, a definite swelling had become noticeable at the left side of the base of the neck, a small nodule had appeared over the right hip and another over the right frontal region. In April, the patient's left eye was noticed to be becoming increasingly prominent, while just before admission a nodule appeared in the left occipital region at a point where the patient had struck her head against the bed-post about three weeks previously.

Physical examination showed a moderately emaciated, middle-aged, bed-ridden woman. The scalp showed a hemispherical, fluctuating swelling about 4 cm. in diameter fixed to the underlying tissue in the right frontal region; a similar smaller nodule in the left occipital region. There was protrusion of the left eye with limitation of motion in all directions and complete loss of vision. The right eye was normal except for a slight congestion of the fundus; the left showed a definite primary optic atrophy. There was lagging

of the left faucial arch and laryngoscopic examination showed fixation of the left vocal cord.

There was a hard, nodular, irregular swelling in the middle of the left side of the base of the neck, displacing the trachea to the right. The mass was about 7 cm. by 4 cm. in size, moved with deglutition, and the veins overlying it were turgescient. There was no cervical adenopathy.

In the vault of the left axilla was a hard, smooth mass about the size of a hen's egg, fixed to the surrounding structures. Just above the level of the scapular spine in the left paravertebral region was an immovable, non-tender, fleshy mass about the size of a walnut. There was some tenderness on pressure along the dorsal spine. Percussion showed an increase in the retromanubrial dulness on the left side. Auscultation showed harsh breathing at the bases and an occasional moist rale at the apices. The heart and blood vessels were essentially negative.

The abdomen showed turgescence of the superficial veins. There was a small, hard, freely movable nodule over the right hip near the posterior superior spine. The liver was not enlarged but was harder than normal. No intraabdominal masses could be felt.

Vaginal examination was essentially negative. Rectal examination showed a soft, round, smooth mass about the size of a plum in the anterior rectal wall, moveable upon the underlying tissues.

Laboratory Findings. The blood counts showed a slight anemia and a slight polymorphonuclear leukocytosis. The blood Wassermann, blood chemistry and urine examinations were all essentially negative.

Roentgen-ray Findings. The skull showed bone absorption in the posterior portion of the right frontal region and in the left half of the occipital bone. The spine showed no change. The left scapula showed destruction of the glenoid fossa and of the body adjoining it. The right showed slight absorption in the outer end of the acromion. There was a small amount of bone absorption in the middle of the shaft of the right humerus and a moderate amount of destruction of the heads of both radii. The left femur showed a small area of absorption at the upper and at the lower end of the shaft. The pelvis showed almost complete destruction of the descending ramus of the right pubis and the ramus of the ischium. The chest showed a dense, sharply circumscribed shadow, about 7 cm. in diameter in the left apical region with apparently complete destruction of the posterior portion of the fourth rib in this region. On the left side there was a large mass, 4 cm. in diameter, just outside the hilus glands. On the right side a fainter shadow extended from the level of the sixth to the eighth ribs to the axillary region with complete destruction of the eighth rib. There were a few small masses scattered throughout the right lung. The superior mediastinum showed a marked increase in width evidently due to an intrathoracic goiter. (Fig. 1.)

Clinical Course. There was gradual increase in the weakness, dysphagia, and dyspnea. The mass at the base of the neck and all the metastases showed progressive growth as demonstrated by palpation and by roentgen-ray studies. On August 31, 1924, the patient developed a flaccid paraplegia with clinical signs pointing to a level at the eighth dorsal segment. From this time onward the course was rapidly downward marked by distention, rectal and vesical incontinence and severe prostration with exitus on September 8, with a terminal pneumonia.

Autopsy Findings. Autopsy was performed one and a half hours after death by Dr. David P. Seecof who furnished us with the following report.

Body is that of a slenderly built, markedly emaciated, middle aged white woman.

Abdomen. Stomach and small intestine are negative. The colon presents several small nodules up to 1 cm. in size at the tips of the appendices epiploicæ, made up of grayish, translucent, congested tissue. In the anterior wall of the rectum, 8 cm. from the anus, is a globular mass about the size of a plum, lying between the muscular and the peritoneal coats and consisting, on section, of a grayish, translucent material.

Pancreas. Along the upper border are numerous grayish, globular, translucent bodies from 0.5 to 1 cm. in diameter.

Liver. On the anterior surface are several round, grayish, translucent tumor nodules, the largest 2 cm. in diameter, only slightly elevated above the general surface and not umbilicated. On section there are seen several nodules similar to the above from 1 cm. to 5 cm. in diameter, some showing a yellowish, central necrosis.

Spleen. Normal in appearance and consistency.

Kidneys. Many slightly elevated tumor nodules 2 mm. to 12 mm. in diameter, not adherent to the capsule, which on section are found to be similar to those in the liver. Pelves, ureters and vessels are normal.

Adrenals. Right: In the center is a grayish, globular, circumscribed translucent nodule 1.5 cm. in diameter. Left is negative.

Pelvic Organs. Bladder, uterus and ovaries are essentially negative.

Chest. Lungs, Right: Scattered throughout the depths of all three lobes are numerous globular nodules from 2 mm. to 5 mm. in diameter. Left: Projecting from the lower lobe at about the middle of the interlobar fissure is a globular mass 3 cm. in diameter. Near the lower part of the upper lobe immediately beneath the pleura are several nodules 1 cm. to 3 cm. in diameter. On section these nodules are all grayish, circumscribed and translucent.

Heart. The endocardium all over is smooth and glistening. Several small polypoid nodules are attached to the endocardial layer on and between the muscoli pectinati, apparently not invading

the muscle layers. The largest of these, 5 mm. by 3 mm. by 2 mm. is situated near the tip of the auricular appendage; the smallest 2 mm. by 3 mm. in diameter, is almost completely hidden behind the muscle bundles. All appear as smooth, globoid, translucent bodies. One nodule 8 mm. in diameter is situated in the center of the interventricular septum, 2 cm. below the bases of the aortic leaflets (Fig. 2.)

Neck Organs. The esophagus, larynx and trachea are displaced to the right and their walls flattened although in no place infiltrated by the enlarged left lobe.

Thyroid. The right lobe is normal in size and situation, measures 3.5 cm. by 3.5 cm. by 0.7 cm. and weighs 5 gm. The isthmus is well formed and in its depths contains a hard, circumscribed nodule 1 cm. in diameter. The left lobe is roughly egg-shaped, measures 11 cm. through the poles, 6 cm. laterally and 7 cm. anteroposteriorly and weighs 120 gm. The lower two-thirds of its volume lay behind the clavicle and the first rib, the lower pole reaching the level of the first interspace 2 cm. to the left of the sternum. It is all over well encapsulated and not adherent to the overlying cervical tissues. Its surface is slightly lobulated and the consistency fairly uniform throughout. On section, the tissue is all over more or less translucent except for scattered irregular areas of opaque, yellowish, slightly granular necrosis. The nodule in the isthmus is a circumscribed translucent structure, not connected with the left lobe, made up of a densely fibrous and hyalinized capsule 1 mm. to 2 mm. thick, enclosing a small amount of dark semifluid material and foci of hyalinized fibrous tissue. Parathyroids are normal.

SKELETAL SYSTEM. Ribs. On the left side the medial portions of the second to the fifth and the seventh and eighth ribs are replaced by large, soft tumor masses. Some of these are situated at the junction of the ribs with the spine; others project into the thoracic cavity but in no place invade the parietal pleura. On the right side there are several small nodules on the inner surface of the upper ribs. On section, the masses in the ribs on both sides consist of hemorrhagic colloidal material of a granular nature.

Vertebræ. The third and fourth thoracic vertebræ are replaced by a large, soft, purplish mass extending 10 cm. to the left and posteriorly forming a prominent mass in the left paravertebral region.

Scapula. A large, soft, well encapsulated mass in the left axilla is found growing from the upper, outer angle of the left scapula. On section, it consists of a soft colloidal material similar to that in the rib metastases.

Skull. Underlying the prominent masses in the scalp in the right frontal and the left occipital region, tumor tissue similar to those in the ribs has completely replaced the bone and lies upon but does not invade the dura.

Left Orbit. Floating free in the orbital fat is a pinkish-gray, soft translucent mass, 3 cm. in diameter, not attached to the orbital walls, displacing the eyeball forward and lengthening and slightly thinning the optic nerve.

Brain and Cord. Near the medial anterior angle of the floor of the left middle fossa growing in the inner surface of the dura is a hard, globular mass 0.5 cm. by 1.5 cm. in diameter, which on section is found to be made of a yellow-white tissue. Brain is negative.

The tumor tissue adherent to the outer surface of the dura, at the level of the third and fourth thoracic vertebræ has not extended through this covering, although the cord in this region is thinned out and softened.

Microscopical Examination. Thyroid. The tumor, which is sharply differentiated from the neighboring normal tissue, consists of solid, interlacing columns of cuboidal cells with clear, vesicular nuclei, showing no alveolar differentiation. Some bloodvessels contain what appears to be normal colloid within their lumina; others show the presence of tumor cells interspersed with red blood corpuscles. (Fig. 3.)

Lung. The tumor mass completely replaces the normal lung markings, anthracotic particles within the tumor showing the remains of the original lung tissue. No differentiation into alveoli can be seen. (Fig. 4.)

Heart. Nodule is composed of small columns of cells similar to those in the thyroid, lying between the endocardium and the myocardium and sharply differentiated from both.

Liver. There is well marked differentiation into alveoli of various size containing colloid. These are scattered irregularly throughout the tumor mass, there being areas composed of undifferentiated solid strands of low columnar cells. (Fig. 5.)

Pancreas. Solid cell masses with no alveolar differentiation.

Rectum. Solid cell masses with an occasional suggestion of an attempt at alveolar differentiation.

Kidney. Metastases solid, same as lung, but largely necrotic. Where preserved, no alveolar differentiation can be observed.

Dura. Tumor shows considerable differentiation into alveoli containing colloid, but they are not as well shaped as those in the liver.

Bone. There is a definite attempt at alveolar formation, there being areas of various size and shape lined with low columnar cells and filled with a colloid like material.

Comment. As Balfour³ has pointed out, a negative history does not rule out the previous existence of pathology in the thyroid gland. In only 1 of our cases was there a definite history of thyroid enlargement previous to the onset of clinical symptoms of malignancy. In the others it was impossible to establish the absence



FIG. 1.—Roentgen-ray of chest showing large intrathoracic thyroid tumor and destruction of left fourth rib by mass in the paravertebral region. Smaller masses in the right apical region and in both hilus regions.



FIG. 2.—Heart showing small tumor nodules between the musculi pectinati in the auricular appendix.



FIG. 3.—Showing the presence of an embolus of cancer cells within the lumen of a venule.



FIG. 4.—Showing extension of tumor cells through bloodvessel wall. This can best be seen at the upper right corner.

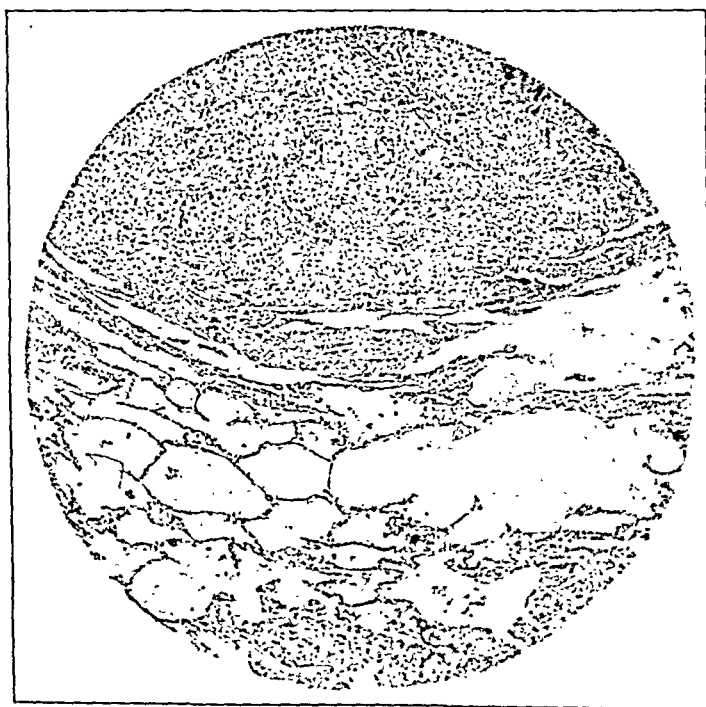


FIG. 5.—Nodule in lung showing the solid undifferentiated type of metastasis.

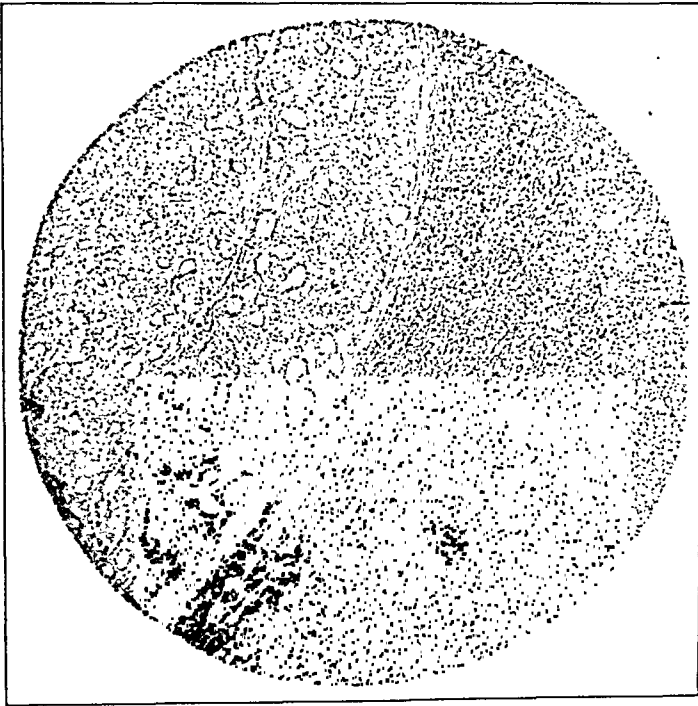


FIG. 6.—Metastasis in liver showing characteristic thyroid alveoli.

of a preceding lesion. In Case VII, particularly, in spite of careful questioning, no history of any enlargement of the neck preceding the onset of clinical symptoms of malignancy could be obtained, and yet, it is more than likely that the circumscribed nodule found in the isthmus, which seems to have given the first symptoms of the disease, had existed quiescently for a long time and that the patient had been made aware of its presence only when it had begun to undergo malignant growth.

Dysphagia, dyspnea and voice changes, all of which occurred early in 5 of our 7 cases, are due to local compression and usually form the first symptoms of the disease.

It is interesting to note that pain, which is usually looked for as an early diagnostic symptom, occurred early in only 1 of our cases, that local fixation occurred in all but 2 and that cachexia occurred in only 1 patient who had had a tracheotomy.

The exophthalmos noted in Case VII. was entirely an incidental occurrence due, as autopsy subsequently showed, to a retrobulbar metastasis and in no way related etiologically to the type occurring in Graves' disease.

The occurrence of malignant change in abnormally situated thyroids has often been noted. Cases have been reported by Huguenin,⁵ Greensfelder and Bettman,⁷ de Graag⁸ and others. Four of our 7 cases had intrathoracic thyroids. This comparative frequency of malignancy in aberrant thyroids is so striking as to suggest forcefully the possibility that abnormality of situation of the thyroid in some way predisposes to the development of malignant change, somewhat analogous to a similar predisposition noted in undescended testicles.

Paraplegia, as a complication of carcinoma of the thyroid, is uncommon. Cases have been reported by Huguenin, de Graag, Skversky and others. Its onset is, in some way, connected with the lodgment of metastatic emboli in the body of a vertebra, although at autopsy, there is seldom to be found any sign of cord compression. The direct cause of the paraplegia, whether it be chemical or neurotoxic in nature is, as yet, unknown. In Case VII, however, it was brought about in an unusual way by the extension of a metastasis, evidently in the left fourth rib, along the rib to the corresponding vertebra with its invasion and pressure upon the cord. Rather noteworthy is the long duration of the root pains—nine months previous to the onset of the paraplegia. It is also rather remarkable that the roentgenological evidence of spinal involvement was so slight that even when the paraplegia was well marked, the roentgenologists could not report any findings suggestive of any destruction of the vertebræ. This was probably due to the fact that the extrathoracic mass in the left paravertebral region effectually hid any pathology in the spine at the same level. This emphasizes forcefully the fact that especially in dealing with more than one shadow

in the same plane, the diagnostic powers of the roentgen-rays are not infallible and must, in a contingency, yield to clinical evidence.

The part played by trauma in determining the site of formation of metastases is problematical. Regensburger found 9 cases of cancer of the thyroid in which local trauma preceded the development of a metastasis. Kaufmann⁹ mentions a case in which a metastasis seems to have developed on the site of a fracture of the femur. In Case VII, the history of trauma in the left occipital region three weeks previous to the development of a metastatic nodule in that situation, suggests the possibility of an etiological relationship between the two.

As to why metastases are numerous and almost ubiquitous in some cases (Case VII) and absent (Cases IV and V) or else confined to a solitary nodule in others, little explanation can be offered. Cohnheim¹⁰ believed that their occurrence was determined by the individual resistance of the host. It is also somewhat difficult to explain the observation that metastases to the lung parenchyma, where they are believed to lodge first, usually remain small while the metastases in the bones grow rapidly. The explanation is probably bound up in the hypothesis that the lungs, in some way, offer poor soil for the development of this type of malignancy while the bones offer less resistance.

That cancer of the thyroid may metastasize by the blood as well as by the lymph stream was affirmed by Kaufmann as long as forty-five years ago. Recent studies have shown that hematogenous dissemination may occur in other types of cancer, but in carcinoma of the thyroid this mode of transmission is so frequent as to be almost the rule. The cause of this has not been explained. Possibly it is due to some peculiarity in the histological relationship between the bloodvessels and the acini in the thyroid gland. In Case VII there was no evidence whatever of any lymph-borne metastases, while beautiful evidence of dissemination by the blood stream was afforded by the occurrence of metastases in the ductless and other highly vascularized glands and by the actual demonstration of colloid and cancer cells in the bloodvessels of the primary tumor. The presence of metastatic nodules in the endocardium is an additional striking illustration of the same phenomenon.

The occurrence of metastases in the heart from a primary focus anywhere is very rare. Perlstein¹¹ mentions 19 cases of cancer of the heart in 9597 routine autopsies reported by Bryant in Baltimore and by Karrenstein in Berlin. Where the site is mentioned these all involved the pericardium or the myocardium; none occurred in the endocardium. Aschoff¹² mentions that cancer of the thyroid may metastasize to the heart and illustrates a melanotic tumor of the endocardium, but I could find no recorded instance of a metastasis to the endocardium from a primary carcinoma of the thyroid. The

rarity of cardiac metastases is probably due as Adami¹³ has pointed out, to the fact that the heart, more than any other organ, is constantly in a state of efficiency, good nourishment and activity, hence does not allow the occurrence of aberrant growths.

Worthy of note is the occurrence of a different histological structure in the metastases in different situations, showing undifferentiated cell masses in the kidney, lung, etc., definite alveolar differentiation in the liver and the dura and an attempt at alveolar formation in the bones and to a lesser extent in the rectum. The cause of this differentiation is difficult to explain. It is not due to a difference in environment as was once thought, since different histological structure has been observed even on the same slide. Eberth thought that alveolar metastases in carcinoma of the thyroid represented a second generation, being produced by the primary metastases and thus forming a reversion to normal type, although Huguenin has pointed out that these alveolar metastases, in spite of their benign appearance, are actually more malignant than the solid type.

The question of the presence of function in metastatic tissue has long been the subject of dispute. As has been pointed out, it is only in cases of cancer of the thyroid that this can be determined since here only, in the characteristic power of thyroid tissue to pick out and fix iodine, have we a measurable criterion by which to estimate function. Ewald and Gierke claimed to have found iodine in metastases from carcinoma of the thyroid, thus tending to prove that they function as normal thyroid tissue. Marine and Johnson¹⁴ however, in estimations upon 3 cases of thyroid carcinoma found practically none in the metastatic tissue and in estimations upon our Case VII, Dr. Marine was unable to find even a trace of iodine in the primary tumor or in the metastases, although the normal portion of the thyroid was found to be almost saturated with iodine.¹⁵ These results point to an absolute absence of function in metastatic tissue and fall in well with our ordinary conceptions of the biology of a cancer cell.

Treatment. The present status of surgical treatment for malignant disease of the thyroid has been well summarized by Balfour who writes on the basis of an experience with 103 cases at the Mayo Clinic. In these, 70 per cent of the successful operations occurred in patients in whom the malignancy was an unexpected finding. When the disease is sufficiently well marked to make the diagnosis fairly definite the results of surgical treatment are discouraging. It is interesting to note in this connection, the apparent cure in Case V, by operation performed one year after the clinical onset of the disease. Radiotherapy seems to be of some value in inoperable cases and as an adjunct to the surgical treatment.

Summary. Seven cases of malignant tumor of the thyroid are analyzed—1 sarcoma and 6 carcinomata. Of these, 1 patient

shows healing of a spontaneous fracture from a metastasis from a sarcoma of the thyroid and is alive and about his work three and a half years after the clinical onset of the disease. Another, after a lobectomy performed one year after the clinical onset of the disease is apparently well with no sign of recurrence two years after the operation. One patient showed an unusually wide distribution of the metastases and developed a paraplegia. At autopsy this was found to be due to a metastasis lodged in the vertebral column as an extension process from a metastasis in the rib. This had caused definite vertebral destruction and cord compression, but did not show up on the roentgen-ray plate during life. In this case, there was no evidence clinically or pathologically of any lymphatic dissemination. Hematogenous dissemination was illustrated by the actual demonstration of cancer cells in smaller bloodvessels of the primary tumor and by the presence of metastases in the endocardium. The latter is a rare finding. No similar case has been found in the literature. The metastases in the different organs showed a different histological structure with reference to the presence or the degree of alveolar differentiation. No evidence of function as determined by the power to fix iodine could be found either in the primary tumor or in the metastases.

I am indebted to Dr. David Marine for his contribution to this paper and to Dr. Isaac Levin for permission to publish this paper from his service.

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THE KOTTMAN REACTION IN THYROID DYSFUNCTION.:

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To attempt to define the various types of thyroid dysfunction, using the clinical picture alone, is often confusing. Classification should be made on the basis of criteria much more definite than physical signs yield. Otherwise, we may have endless discussion that leads to conclusions anything but conclusive. As laboratory methods advance and progress, however, we begin to see in them the solution to this problem.

Thyroid dysfunctions now may be studied by any of the following methods: (1) Basal metabolism; (2) Goetsch test (adrenalin); (3) serologic tests for thyroid secretion. The first two methods we will not consider in detail. Of serologic tests, we may have two kinds: (1) The complement-fixation reaction; (2) the Kottman test.

The purpose of our studies was to discover whether we could get positive results in known thyroid cases when using the Kottman test, and in addition to see how the results of this test compared with those of basal metabolism.

Principles of the Test. This test, evolved by Kurt Kottman of Switzerland, is based on a two-fold theory: (1) That one colloid has a protective property for another colloid; (2) that a photosensitive substance reacts more to the light in fine suspension than in coarse suspension.

When silver nitrate is added to potassium iodid in the presence of human serum, the result is a cloudy mixture. There has been formed silver iodid, which is held in colloidal suspension by the serum which is itself a colloid. In sera, the protective power for another colloid varies. It is strongest in hyperthyroid serum, weakest in hypothyroid serum and intermediate in normal serum. In other words, the suspension of AgI in hyperthyroid serum is very fine, less fine in normal serum and relatively coarse in hypothyroid serum. Now, when the colloid is exposed to the light and the developer (in this case hydroquinon) is added, the reduction to metallic silver varies inversely with the fineness of the particles in the suspension. Therefore the change from AgI to metallic Ag is greatest in the hypothyroid serum, and least in the hyperthyroid serum. Since this chemical change is evidenced by a change to a brownish color, we have a simple index to the degree of secretion. In hyperthyroidism there is little change in color, in hypothyroidism the color changes fairly rapidly to a brown that is almost black, while in normal serum, the change comes half-way between these two extremes.

Technique. 1. Five cc of blood is withdrawn from the vein by the usual method.

2. The blood is centrifugalized to obtain the clear serum.

3. To 1 cc of clear serum is added 0.25 cc of potassium iodid solution (0.5 per cent) and 0.3 cc of silver nitrate solution (0.5 per cent).

4. Mix thoroughly and carefully by shaking.

5. The colloidal suspension of silver iodid formed by this mixing is exposed for fifteen minutes to a 500-candle power light held at a distance of 25 cm.

6. To the suspension is added 0.5 cc hydroquinon (0.25 per cent) solution.

7. Readings are taken every five minutes for thirty minutes. For convenience, we grade the color changes from zero to 4+.

These are the only conditions which are absolutely essential. There are others, however, which if observed, make for greater accuracy, and so reduce the possible sources of error. The best and most reliable results are obtained when the patient has fasted for twelve hours before the blood is taken. Bromids used within two months before the time of the test will retard the reaction. Should the patient have taken bromids, due consideration should be given this fact in noting the result. The blood should be used as soon as possible after it is withdrawn. It is best to add the KI and the AgNO_3 in a dark room using a red light. This same precaution should be observed when the hydroquinon is added to the AgI. And last, but by no means least, blood serum from a normal individual should be used as a control.

Interpretation of Readings. From our studies and our observation of what we assumed to be normal cases, we considered a normal reaction one in which there are some evidence of color change within the first five to ten minutes and then a gradual deepening of this color to a definite dark brown within thirty minutes. When there is hypersecretion the reaction or color change is considerably retarded. At first there may be no apparent change. Even at the end of the prescribed period of observation there may be only a slight darkening. When the change comes quickly and there is a brownish discoloration in the first five minutes, this color rapidly becoming darker until it approaches black, we consider that here we have deficiency of thyroid secretion.

Discussion. Our studies with the test were made in three groups: (1) Hyperthyroid cases; (2) hypothyroid cases; (3) general conditions. This last group was included to determine how the Kottman test results compared with the readings of the basal metabolism tests.

Unfortunately, our thyroid case material was not so extensive as others, who have worked with this test, have reported. Out of 100 cases there were available only 14 patients who were observed for the effect upon goiter and hyperthyroidism.

TABLE I. THYROID CASES.

No.	Name.	Thyroid.	Von Graefe.	Tremors.	Basal metab.	Kottman reaction, minutes.						Result.	Remarks.
						.5	10	15	20	25	30		
I	F. P.	Enlarged	Present	Absent	+13	+	+	+	++	++	++	Slight retarded	A previous reading was +24.
II	M. L.	Palpable	+	○	+14	○	⊕	⊕	++	++	⊕	Slight retarded	
III	E. T.	Enlarged	○	+	+54	⊕	⊕	⊕	++	++	++	Retarded	
IV	M. S.	Enlarged	+	+	+20	⊕	⊕	⊕	++	++	++	Retarded	
V	I. R.	Enlarged	+	+	+25	⊕	⊕	⊕	++	++	++	Retarded	
VI	M. M.	Enlarged	+	○	+20	⊕	⊕	⊕	++	++	++	Retarded	
VII	A. M.	Enlarged	○	○	+14	⊕	⊕	⊕	++	++	⊕	Retarded	A previous reading was +75.
VIII	M. J.	Enlarged	+	○	+51	⊕	⊕	⊕	⊕	⊕	⊕	Retarded	
IX	A. G.	Enlarged	+	+	+18	⊕	○	⊕	⊕	⊕	⊕	Retarded	
X	I. E.	Enlarged	+	+	+19	○	⊕	⊕	++	++	++	Retarded	
XI	C. B.	Enlarged	+	+	+21	+	+	+	++	++	+	Normal	
XII	M. B.	Palpable	+	○	+18	○	○	+	++	++	++	Retarded	
XIII	F. P.	Enlarged	+	○	+21	○	+	+	++	++	++	Slight retarded	Unexpected reaction.
XIV	R. O.	Palpable	+	○	+18	○	○	○	⊕	⊕	⊕	Retarded	

○ = no color change.

⊕ = doubtful.

+ = light brown.

++ = brown.

+++ = dark brown.

++++ = black (or a very dark brown.)

I should mention that these were not necessarily early cases of exophthalmic goiter. Case I, for example had an enlarged thyroid, with exophthalmos. There were no tremors of the outstretched hand. The patient was operated upon two years before when part of the thyroid was removed. The metabolic rate was +13, which is only a slight elevation above the normal limit. The Kottman test showed a slightly retarded reaction.

With the exception of C. B., No. XI, the blood test tallied with the basal metabolism results. Here (C. B. No. XI) we are dealing with a frank exophthalmic goiter of one year's duration. The patient is a white female, aged twenty-nine years. Despite constant medical care and roentgen-ray therapy, her condition had progressed with the usual effect upon the heart. The patient's condition was so poor that I hesitated to make any blood studies that might excite her. After the exophthalmos subsided, the damaged heart was beyond repair. The goiter, von Graefe, and tremors still persisted. It was at this time that the Kottman test was performed. The result was, surprisingly, a normal reaction. This reading may be looked on in two ways. The first instinct is to feel that the test has failed. On the other hand, we may consider that our knowledge of the thyroid being still incomplete, it might be possible that an overactive gland ceases to throw off excessive amounts of thyroid secretion. Occasionally we do see cases in which there is a swing from a state of hyperactivity to deficient secretion of thyroid substance. If this is true, then the Kottman has an added value because it gives us information of the gland's activity which we do not, as in this cited case, get from the misleading clinical picture.

D' Houbler, in a series of 58 cases of exophthalmic goiter, had a similar experience. In all but 1 of his cases, the Kottman reaction indicated a state of excessive secretion. In the exceptional case, there was seen an accelerated reaction such as we find in hypothyroid cases.

Peterson and his coworkers, in a series of 70 cases, found the test lacking in only 3 instances. In 1 case there was an accelerated reaction and in the other 2, normal reactions.

Hypothyroid Group. Two patients with definite evidences of hypothyroidism were studied with the following results:

	Thyroid.	von Graefe.	Tremors.	Basal.	Kottman.
I T. D. . . .	Not palpable	0	0	-20	++++
II S. B. . . .	0	0	0	-14	⊕⊕⊕⊕

The first case showed a markedly accelerated reaction, such as we might expect in this condition. Case II who was admitted as a case of myxedema, showed a retarded reaction. This unexpected result might be explained by the fact that this patient had been treated with thyroid substance for several days prior to the taking

TABLE II. A COMPARISON BETWEEN THE READINGS OF THE KOTTMAN TEST WITH THE BASAL METABOLISM IN MISCELLANEOUS CONDITIONS.

No.	Name.	Evidence of thyroid dysfunction.	Basal metab.	Kottman reaction, minutes.						Result.	Diagnosis.	Remarks.
				5	10	15	20	25	30			
I	R. G.	None	+9	+	+	+	+	+	+	Normal	Cardiac	(Convalescing).
II	D. P.	Exophthalmos	+8	+	+	+	+	+	+	Normal	Pneumonia	
III	R. A.	None	+1	+	+	+	+	+	+	Normal	Neurasthenia	
IV	J. G.	Slightly enlarged thyroid; coarse tremors	+10	⊕	+	+	+	+	+	Normal	Vasomotor ataxia	
V	A. S.	None	+6	+	+	+	+	+	+	Normal	Nephritis	(Presumably of endocrine origin). (Symmetrical).
VI	R. O.	Von Graefe, tachycardia	+64	○	○	○	⊕	⊕	⊕	Retarded	Psychasthenia	
VII	A. C.	After 3 weeks rest	+18	⊕	⊕	⊕	+	+	+	Retarded	Tachycardia	
VIII	N. R.	None	+4	+	+	+	+	+	+	Retarded	Lipomatosis	
IX	G. D.	None	+17	+	+	+	+	+	+	Normal	Diabetes	High-strung. Very high-strung.
X	S. E.	None	+9	+	+	+	+	+	+	Normal	Diabetes	
XI	B. H.	None	+8	+	+	+	+	+	+	Normal	Diabetes	
XII	M. V.	Tremors	+30	+	+	+	+	+	+	Slightly accelerated	Diabetes	
XIII	S. E.	None.	-1	⊕	⊕	⊕	⊕	⊕	⊕	Retarded	Diabetes	Hypertension. Hypertension.
XIV	M. J.	Slightly enlarged thyroid tremors	+19	+	+	+	+	+	+	Slightly retarded	Diabetes	
XV	S. W.	Palpable thyroid, no toxicity	+21	+	+	+	+	+	+	Slightly retarded	Diabetes	
XVI	S. Z.	Von Graefe	+11	+	+	+	+	+	+	Retarded	Diabetes	Thyroid gland had been given.
XVII	A. G.	None	+14	⊕	⊕	⊕	⊕	⊕	⊕	Retarded	Diabetes	
XVIII	S. B.	Slightly enlarged thyroid	+11	⊕	⊕	+	+	+	+	Retarded	Diabetes	
XIX	T. D.	None	-20	+	+	+	+	+	+	Accelerated	Nephritis	Thyroid gland had been given.
XX	S. B.	None	-14	⊕	⊕	⊕	⊕	⊕	⊕	Retarded	Myxedema	

of blood for Kottman reaction. Although we knew of this, we were curious to discover what the result would be under the circumstances.

The retarded reaction was quite possibly due to the excessive amount of thyroid substance present in the blood stream as the result of the thyroid administration. Peterson and colleagues noted this same fact when in their experiments with dogs, they administered thyroxin.

Comparative Study of Basal Metabolism. *Tests with Kottman Reaction.* Table II was arranged to show how the Kottman reaction results checked with metabolic readings in order to determine how reliable a test the former may be considered. Of the 20 cases tabulated in Table II, we find four discrepancies between the two results (Nos. IX, XII, XIII, XX). Table I shows one other, Case No. XII—C. B. The total number of cases, then, where we find no check between the two tests, is 6, out of the total of 34 cases which were studied. It would be unfair to the Kottman test to condemn it for these failures without first giving due consideration to certain aspects of each of these cases.

Case IX, G. D., clinically showed no evidence of thyroid dysfunction, yet the basal metabolic rate was +17.

Case XII, M. V., likewise showed +30 with no other manifestation than tremors.

Case XIII, S. E., a high-strung individual with a definitely retarded Kottman reaction indicating hypersecretion, showed a -1 basal rate.

These patients, it should here be noted, were all diabetics.

The remaining 2 cases, No. XX, S. B., diagnosed myxedema, and No. XII, C. B. (Table I), diagnosed exophthalmic goiter, have already been discussed.

Reviewing these cases and taking into consideration the clinical picture, it seems unfair to use as evidence against the Kottman reaction, the failure of Nos. IX, XII, XIII to coincide with the metabolic result. It is possible that these very discrepancies might indicate the repeating of the basal metabolism test to confirm the first readings. The case for the Kottman reaction might have been made stronger if these confirmatory tests had been done. It is unfortunate that this was not done, for the personal equation enters so largely into the metabolism test that quite possibly we could have gotten results more compatible with the Kottman results. So often the technician, conducting the metabolic studies, is hampered by either the lack of intelligence, or by the nervousness of the subject. Despite all the precautions, these factors may bring about a higher reading. If we accept these in considering our results we may, then, narrow down the number of discrepancies to 2 cases in the miscellaneous table and 1 in the thyroid table which is by no means a poor showing for the still unrecognized Kottman reaction.

When we reach the point where we can definitely say that this

test is reliable, its advantages over the basal metabolism test can easily be demonstrated. The technic which is simple, calls for no expensive or cumbersome apparatus. The unreliable element of the patient's emotional state or temperament cannot influence the result. It may be used for those patients who cannot be moved. Unmanageable patients or those without teeth to grip the mouth-piece of the metabolic apparatus, can be tested in this way without undue annoyance to either patient or physician.

Conclusions. From our studies with the Kottman reaction and from a comparison of its results with that of the basal metabolism tests, we feel that this method of measuring the degree of thyroid secretion can be said to be of value. We found, with our limited material, that the test is consistent (with only an occasional exception) in thyroid dysfunction (particularly hyperactivity). We found also that, except in a few cases, our test checked up with the basal metabolism results.

This test, if recognized as proven, would be valuable for the following reasons:

It is simple in its technique and apparatus.

It would be a very good substitute when basal metabolic readings are not so easily obtained.

It would, because of its simplicity, be an excellent measure for checking results obtained by the basal metabolism test.

Unless this test can be shown to be absolutely inaccurate and worthless, I believe it should be given a fair trial. Sufficient studies have not yet been made to permit us to decide whether it should rank with such proven tests as basal metabolism and the Goetsch test. I think that it has merit enough to warrant its being used in clinics where there is abundant thyroid material. It is only in this way that its reliability can actually be determined and its value proved.

I wish to express my thanks to Jacob Wollen who assisted me in collecting experimental data for this study.

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FURTHER STUDIES OF CEREBROSPINAL FLUID IN INFANTS AND YOUNG CHILDREN.*

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(From the Babies' Hospital, New York City.)

Normal Infants and Children. For comparison with the data furnished by lumbar puncture in various diseases, the following will be considered as normal cerebrospinal fluid—clear and colorless, slightly alkaline in reaction, specific gravity approximating 1002. Pressure is disregarded in the age group under consideration as it is greatly influenced by crying and muscular movements, and these cannot be controlled in infants. Globulin does not exist in demonstrable quantities in the normal cerebrospinal fluid of infants; when a definitely positive globulin reaction is present the fluid is pathological. Lymphocytes are normally the only cells present in cerebrospinal fluid; as many as 20 per c.mm. may be found in a normal child.

There is nearly always a positive reaction for a reducing substance, dextrose, which varies in amount as determined by the Folin and Wu method, between 45 and 85 mg. per 100 cc of fluid.

The chlorids are so variable, 600 to 750 mg. per 100 cc of fluid, that any constant relationship in their amount to any of the meningeal or extrameningeal infections has not been determined by us.

Cerebrospinal Meningitis. Thirty-five cases of cerebrospinal meningitis are presented, 23 of which were proved by the isolation of the meningococcus from the blood or cerebrospinal fluid and 12 by the clinical course and response to specific serum therapy in addition to changes in the cerebrospinal fluid. Many of these patients were admitted in a moribund condition. Eleven were discharged from the hospital cured of the condition for which they were admitted, 7 were improved and 17 died, of which 3 came to autopsy.

These cases were from one month to four years of age, 13 were not over six months of age and 25, or 71 per cent, were not over one year of age. This is a striking commentary on the age incidence of the sporadic type of meningococcus infection. It seems probable that because of the mild character of the symptoms in many cases in infancy a number of such infections remain unrecognized. In not a single instance was a clear fluid obtained by the first

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lumbar puncture, although in 4 instances the cell count was less than 500 per c.mm. One specimen of fluid from which meningococci were obtained contained only 100 cells, yet was slightly turbid due to fibrin. In most instances the fluid was described as turbid, but in 2 patients with counts over 10,000 it was frankly purulent in character. In a few cases the globulin test was not recorded. In all the others it was positive.

In 29 cases in which a qualitative test for sugar was done it was negative in 24 cases, faintly defined in 1 and in 4 cases definitely positive. Since the meningococcus possesses the power of fermenting glucose it naturally follows that a diminution of the sugar content of the cerebrospinal fluid should be noted in the cases with moderately increased cell counts and a complete absence in the fluids with high cell counts, particularly those with purulent fluids. Along these lines the following may be of interest. In cerebrospinal fluid from 16 patients a quantitative estimation of sugar was made. In the first or second lumbar puncture made after admission to the hospital the fluid in 4 cases contained no sugar, 7 had not more than 26 mg. per 100 cc of fluid and of the remaining 5 cases, 4 were not above 45 and 1 only had a normal content of 65 mg. per cc, which was late in the disease when the cell count was only 110 and the culture showed no growth. These patients were admitted to the hospital during various stages of their infection. It is of interest to note the rise of the curve of sugar, as the number of cells diminish with specific serum therapy.

Case Reports. CASE I.—Patient (25,121), aged four years, is typical. From the first lumbar puncture cloudy fluid was withdrawn which contained 3000 cells per c.mm. and numerous meningococci. The sugar quantitatively was 20 mg. per 100 cc. Specific intraspinal and intravenous serum therapy was commenced immediately, and during the period of hospitalization the sugar was determined quantitatively eight times. There was a gradual rise in the sugar content coincident with the decrease in the number of cells. At the eighth lumbar puncture the cell count had diminished to 36 cells and the sugar had increased to 58 mg. The patient was discharged cured.

CASE II.—E. A. (23,558), aged eighteen months, with 4460 cells and 28 mg. of sugar per 100 cc, showed meningococci in both blood and cerebrospinal fluid; 10 cell counts were made during the period of treatment, at the last puncture but one only 9 cells were present and the sugar had increased to 59 mg. per 100 cc of fluid. The patient was discharged cured.

Of special interest is T. B., Case 24,437, aged one month, who had two lumbar punctures and two cistern punctures while under

observation. In the first puncture 2620 cells were counted and the sugar content was 39 mg. per 100 cc of fluid. No response to serum therapy was observed, and therefore only a slight diminution in the number of cells occurred. The sugar decreased before death to 18 mg. per 100 cc of fluid and the cell count was 1960.

Encephalitis. Nine cases of encephalitis are presented, from six months to five years of age, all but one of whom were discharged as improved of the condition for which they were admitted. In only 5 cases was pleocytosis present; the highest cell count on admission was 220. In 5 of the cases a faint globulin reaction was present. The only constant finding of interest in these cases was a high sugar content, which was noted in 4 of 6 cases in which the chemistry was done. In the other 2 cases the quantitative sugar was in the upper limit of normal. The two following cases are of special interest on account of the chemistry.

CASE III.—T. S. (24771), aged eighteen months, was admitted because of vomiting, drowsiness, rigidity of the neck and convulsions. At the initial puncture clear fluid was withdrawn which showed 220 cells, 80 per cent of which were lymphocytes. The globulin test was negative, and the test for a reducing substance was positive; 108 mg. of sugar per 100 cc was present. Successive counts showed 120, 150, 154 and 37 cells respectively. Successive sugar estimations were 108, 99, 62 and 27 mg. per 100 cc of fluid, which demonstrates very nicely the decrease of the sugar with the disappearance of the evidence of meningeal irritation. The last sugar determination was much below normal, and was obtained from a fluid showing only 37 cells. The patient was discharged cured.

CASE IV.—B. T. (25485), aged three years, showed a persistently high sugar throughout the course of her disease which terminated fatally. She was admitted on account of drowsiness, slurring speech, anorexia and convulsions. She was comatose on admission and remained so during the twelve days' period of observation. The first cerebrospinal fluid obtained was from a cistern puncture. This showed 160 cells with a predominance of polymorphonuclears, a trace of globulin was noted and the test for a reducing substance was positive. The quantitative test for sugar gave 105 mg. per 100 cc of fluid. Four other specimens of cerebrospinal fluid all obtained by lumbar puncture showed only 108, 30, 1 and 2 cells respectively, yet the sugar remained constantly high, 89, 92, 102. The temperature had daily fluctuations between 101° and 105.6°, once reaching 106° F. An autopsy which was performed, December 25, 1924, showed a rather friable brain with no inflammation of its coverings. (It is now in a hardening solution in preparation for further study.)

A predominance of the polymorphonuclear cells in the cerebrospinal fluid of this case may be explained by the fact that the first stage of encephalitis, like the first stage of poliomyelitis, is accompanied by a meningeal irritation which means polymorphonuclear cell increase. A marked leukocytic reaction of the blood in 6 of 7 cases, with an average of 19,600, may be worth recording, but it would not serve as an aid in differential diagnosis since all infections of the central nervous system may at some stage be accompanied by a high white blood cell count.

Encephalitis Due to Lead Poisoning. The following three cases of encephalitis due to lead poisoning seem of sufficient interest to merit attention, especially since poisoning by lead is seldom considered as a diagnostic possibility in infants and young children. These cases will be reported in detail by Dr. F. G. Beal.

CASE V.—R. G., aged four and a half months, was nursed from birth, and thrived until three weeks before admission to the Babies' Hospital. Irritability was then noted, vomiting occurred frequently and eventually twitching of the right arm and the right side of the face was observed. On admission, twitching of the right arm was observed in addition to a bulging fontanel and exaggerated knee jerks. Fever was not present. Routine examination of the blood disclosed marked basophilic stippling of the red cells, and on more complete investigation it was learned that the mother had used lead nipple shields for both breasts since her discharge from the maternity hospital. Lead was found in the mother's milk and in the stools of the infant. The first lumbar puncture showed a clear fluid with 60 cells, a trace of globulin and positive sugar reaction. The third lumbar puncture showed turbid fluid, the first part withdrawn was slightly blood tinged. It contained 70 cells, 80 per cent of which were polymorphonuclears. The reaction for globulin was marked. (Bloody fluids are in nearly every instance discarded at the Babies' Hospital.) The quantitative sugar determination showed 46 mg. per 100 cc. The chlorids were 738 mg. The third puncture showed turbid fluid with 1130 cells, 93 per cent of which were polymorphonuclears. The reaction for globulin was marked. No lead was discovered in the spinal fluid. The infant was discharged cured.

CASE VI.—H. L., a child, aged sixteen months, died after a brief period of observation in the Babies' Hospital. Basophilic stippling of the red blood cells drew attention to the fact that lead poisoning was probably present. The infant's father was a painter; other than this no source could be discovered for the presence of the lead. The organs were removed at autopsy and lead was demonstrated. Only one lumbar puncture was done, which showed 16

cells and a positive globulin reaction. The qualitative reaction for sugar was negative.

CASE VII.—S. K. (24,663), a defective child, aged twenty months, was admitted to the hospital with the statement that for two months he had had a perverted appetite, had eaten paint off furniture, bits of paper, etc. For two weeks vomiting had been noted, which just prior to admission became projectile in character. Drowsiness had been present for a day. This child succeeded in eating considerable amounts of freshly applied enamel from his bed during his early period of hospitalization. Basophilic stippling of the red blood cells was noted. On lumbar puncture a clear fluid was withdrawn which showed 22 cells, 74 per cent of which were polymorphonuclears. The globulin reaction was strongly positive. The quantitative sugar determination was 52 mg. and the chlorids 713 mg. per 100 cc of fluid. Four days later clear fluid was withdrawn by lumbar puncture which showed 26 cells—all lymphocytes. The reaction for globulin was positive. A later puncture showed clear fluid with 15 cells—mostly lymphocytes. The globulin reaction was positive. The spinal fluid had 72 mg. of sugar per 100 cc and 675 of chlorids. The last lumbar puncture showed only 4 cells and 62 mg. of sugar. Lead was found only in his stools. He was discharged improved.

Acute Poliomyelitis. Lumbar puncture was done in 7 cases of poliomyelitis and polioencephalitis, with an average age of nineteen and a half months. Several of these cases were admitted to the hospital a number of days after the acute symptoms had subsided, which accounts for the negative findings in the cerebrospinal fluid. All were discharged improved of the condition for which they were admitted. In the 7 cases the fluid withdrawn was clear and colorless, and in 3 cases only were more than 20 cells found. In 5 cases in which a test for globulin was done it was positive in 4. The test for a reducing substance was positive in the 6 cases in which the test was done.

Chemical analysis for sugar was done in 6 of the 7 cases and showed the amount to be within the normal limits in all. In 4 cases in which a quantitative determination of chlorids was done all were within normal limits.

CASE VIII.—F. M. (23,857), aged nineteen months, who had five different chemical analyses for sugar and chlorids, is an example of the variability shown in the chemistry of the cerebrospinal fluid in this condition. The patient was admitted because of vomiting, irritability and drowsiness, and at the onset and for several days thereafter the working diagnosis was tuberculous meningitis. Lumbar puncture showed clear fluid at each tap with 15, 5, 24, 14 and

4 cells respectively. The globulin test was positive in two out of four examinations. No organisms were obtained by smear or culture of the cerebrospinal fluid. The quantitative determination of sugar gave the following values per 100 cc of fluid: 71, 76, 62, 50, and 101. Four were within normal limits, with one in the lower zone of normal, while one was considerably above normal limits. This child was discharged improved of the condition for which he was admitted.

From the evidence here presented in a small group of cases with chemical findings, and confirmed by earlier observations of a large group of cases without chemical analyses, the only changes in the cerebrospinal fluid which will aid in the diagnosis in the acute stage of the disease is a cellular reaction and a positive globulin reaction.

Tuberculous Meningitis. Nineteen cases of tuberculous meningitis are presented, from seven months to five and a half years of age, with an average age of twenty months. In 16 cases the diagnosis was proved either by autopsy (in 9 cases) or by the discovery of tubercle bacilli in the spinal fluid. In 3 cases the diagnosis was made on the history, the course of the disease in conjunction with the result of the Pirquet test and the findings in the cerebrospinal fluid. In 13 cases tubercle bacilli were found in the spinal fluid. This is a lower percentage of positive fluids than the general results at the Babies' Hospital, to be explained by the short period many of these cases were in the hospital, thus allowing of but one examination of cerebrospinal fluid. No tubercle bacilli were found in the cerebrospinal fluid of Case 25117. At autopsy only recent tubercles were present along the vessels and no fibrinous exudation, which explains the absence of organisms in the cerebrospinal fluid.

Although in several instances more than 300 cells per c.mm. were counted, in every one of the 19 cases the fluid was clear and colorless.

There is an impression, which is a correct one, that lymphocytes are the predominating cell in the cerebrospinal fluid of tuberculous meningitis, especially in the early stages, and that polymorphonuclear leukocytes frequently predominate in the last stage. However, in the 15 cases in this series, in the fluid from the first lumbar puncture lymphocytes predominated in only 6, while in 7 the polymorphonuclears were in excess and in 2 cases the cells were equally divided. Many of the patients in this group were admitted in the later stages of the disease.

There is a wide variability in the number of cells; several cases presented low cell counts, 2 were less than 50 cells and the highest count in any of the 19 cases was 1260 cells.

The cellular reaction seems to bear no relationship to the num-

ber of tubercle bacilli in the cerebrospinal fluid. In 1 case with a cell count of but 20 tubercle bacilli were discovered on the first examination, while in 2 cases, proved by autopsy each with more than 300 cells, tubercle bacilli were not discovered in the cerebrospinal fluid.

In several cases repeated puncture in various stages of the disease failed to reveal a marked cellular reaction. Case 24662, proved at autopsy, showed 28, 84, 30 and 40 cells in four successive lumbar punctures. In 18 of the 19 cases on which a test for globulin was made it was definitely positive in all, and in 13 the reaction was very marked. In 18 cases in which a qualitative test for a reducing substance was done it was positive in 8 cases, faintly positive in 1 and absent in 9.

A quantitative estimation of dextrose was done in 13 cases, 12 of which were proved by autopsy or by the finding of tubercle bacilli in the spinal fluid. In only 1 of the cases was the sugar normal; in 12 it was definitely reduced, of which 3 showed the sugar content to increase toward the terminal stages. The highest dextrose content per 100 cc of cerebrospinal fluid was 75 mg. Several specimens were examined which contained no sugar. The average for the cases in which a quantitative sugar determination was made was 28 mg. per 100 cc. It is thus apparent that there is a definite diminution of dextrose in tuberculous meningitis, which should at least serve as a help in the early differential diagnosis between this disease and encephalitis. It has been maintained by some that the chlorids are diminished, but in the 12 cases in which a quantitative determination of chlorids was made the variability was so wide there is little evidence of any diagnostic value in a chlorid determination. Only extremely rarely at the Babies' Hospital* has a case of tuberculous meningitis came to autopsy in which general miliary tuberculosis was not demonstrated at the autopsy table. In 8 of the 9 autopsies in this series tuberculosis of the meninges was found to be only one lesion of a general miliary tuberculosis.

Pneumococcus Meningitis. In 5 cases of pneumococcus meningitis pneumococci were demonstrated in the cerebrospinal fluid. In 3 of the 5 cases organisms were also found in the blood stream. All of the 5 patients died. The youngest patient was three months of age and the oldest was twenty-nine months. All the specimens of fluid, as would be expected, were turbid, and the average count for the first lumbar puncture taken on admission to the hospital was 980 cells. In every case the globulin was strongly positive. The quantitative test for sugar was similar to the other purulent types of meningitis, that is, consistently low. The average for five examinations showed only 26 mg. per 100 cc of fluid. The average chlorid content for four examinations was 617.

* Wollstein and Bartlett; *Am. Jour. Dis. Child.*, 1914, 8, 362.

Congenital Syphilis. Sixteen infants are listed under this diagnosis—from five weeks to twenty-seven months of age; 6 were under six months. In 7 cases the diagnosis was made on the blood Wassermann reaction alone. In the others, all of whom had positive blood Wassermann tests, it was made either at autopsy (in 5 cases), by florid cutaneous manifestations or by a positive Wassermann of the cerebrospinal fluid. In 13 cases in which the globulin test was done it was positive in 6, faintly positive in 1 and negative in 6. The average cell count, excluding the case of syphilitic meningitis, was 30 per c.mm. Five of 15 cases had an increased number of cells. One infant, with clinical syphilis and a 4+ blood Wassermann reaction, gave a negative globulin test in the spinal fluid. Another clinical case, with 27 cells in the cerebrospinal fluid and a positive blood Wassermann reaction, did not show any globulin in the spinal fluid, but a third case, with a positive Wassermann reaction in the blood and in the spinal fluid, in three examinations gave a negative globulin reaction in one specimen of fluid and extremely faint reactions in two other specimens.

Of 11 patients, all with positive blood Wassermann tests, in whom the diagnosis was made by marked clinical manifestations, by a spinal fluid Wassermann test or by autopsy, only 5 showed an increased number of cells in the spinal fluid—28, 160, 162, 27, and 504 cells, respectively.

It was noted in a previous study of a larger group of cases, and again in this group, that congenital syphilis may involve the central nervous system without showing an increase in the number of cells in the cerebrospinal fluid.

The following case illustrates this point:

CASE IX.—R. C. (24,732), aged eighteen months, was admitted because of drowsiness, muscular weakness and convulsions. The blood and cerebrospinal fluid gave a 4+ Wassermann reaction and 66 mg. of sugar per 100 cc of spinal fluid was found. Lumbar puncture on three different days showed 1, 2 and 2 cells respectively, yet at autopsy a chronic leptomeningitis was found in addition to visceral lesions associated with congenital syphilis. Nor does the severity of the cutaneous or visceral lesions bear any relation to the condition of the meninges, as illustrated by Case 24,998, aged three months, which in addition to a 4+ Wassermann reaction had anasarca, nephritis and syphilitic epiphysitis, yet only 4 cells were found in the cerebrospinal fluid.

A reduction with Benedict's solution was a uniform finding in the cases of congenital syphilis.

In 9 cases in which a quantitative test for dextrose was done it was within the normal in 8 cases and definitely reduced in only 1 case. These findings would lead one to believe that the quantitative estimation of dextrose shows that it is present in normal

amount in nearly every instance of congenital syphilis without meningitis in infancy. In 9 cases in which a quantitative estimation of the chlorids was made all were within the range of normal.

Of unusual interest is the following case of syphilitic meningitis proved at autopsy.

CASE X.—R. G. (23,945), a male infant, aged seven and a half months, was admitted to the Babies' Hospital on account of convulsions, weakness of voice, weakness of left arm, loss of weight and diminished excretion of urine. On lumbar puncture faintly turbid cerebrospinal fluid was withdrawn which showed 504 cells, 80 per cent of which were lymphocytes. The globulin test was strongly positive, the qualitative reaction for sugar was negative. The quantitative sugar determination showed 20 mg. per 100 cc of fluid and 700 mg. of chlorids. One week later lumbar puncture showed 1580 cells, mostly lymphocytes, a positive globulin reaction and a faintly positive reaction for sugar. The quantitative sugar showed 28 mg. and the chlorids 688. A third puncture showed a diminished number of cells and an increase in the quantity of sugar and 610 cells, with 37 mg. per 100 cc of fluid. The blood and cerebrospinal fluid showed a 4+ Wassermann reaction. The mother's blood Wassermann test was also strongly positive. In a precipitate of the cerebrospinal fluid no spirochetes were found. The eye grounds showed a low-grade retinitis. The infant was treated vigorously with neoarsphenamin intramuscularly and intravenously. He was also given arsphenaminized serum intrathecally. Death occurred after six weeks of observation.

Autopsy revealed cerebral hemorrhagic pachymeningitis and cerebral and spinal syphilitic leptomeningitis, in addition to the usual visceral lesions of congenital syphilis.

1. The intensity of the cutaneous manifestations of congenital syphilis is not a criterion of the findings in the cerebrospinal fluid.

2. Congenital syphilis may involve the central nervous system, as proved by a positive Wassermann reaction of the cerebrospinal fluid without causing a cellular reaction in the fluid.

3. A quantitative chemical analysis of the cerebrospinal fluid, for sugar and chlorid, in itself is not a helpful diagnostic item in the diagnosis of neurosyphilis; but taken in conjunction with the other findings it may add another positive point.

4. In syphilitic meningitis there is a reduction in the amount of sugar present in the cerebrospinal fluid, comparable to the reduction noted in other types of meningitis with high cell counts.

Obscure Cases. As evidence of the bizarre types of meningeal irritation not infrequently observed in infancy, particularly in early infancy, the following cases are presented. All were discharged from the Babies' Hospital with the note that they had given evidence of an undiagnosed condition of the meninges.

CASE XI.—H. M. (24,445), aged nineteen days, was admitted on account of convulsions, of which twelve had been noted during the twenty-four hours previous to admission. For a week he had not cried and had refused to nurse. The infant was somnolent. The umbilicus showed a slight discharge. The first lumbar puncture showed a clear fluid with 96 cells, mostly polymorphonuclears. The globulin reaction was sharply positive and the reaction for a reducing substance was positive. Five days later a second lumbar puncture showed slightly blood-tinged fluid with 264 white cells. The day following a cistern puncture showed a clear fluid with 96 cells. Subsequent counts were 176, 80, 28 and 83 respectively. Two quantitative sugar determinations showed a decreased amount, that is, 30 and 37 mg. per 100 cc of fluid. The culture of the blood and spinal fluid showed no growth. The Pirquet test, as would be expected, was negative. The infant was under observation thirty-five days and was discharged cured. He was examined at the age of eight months and was apparently normal. At that time the lumbar puncture revealed only 4 cells with a positive reaction for sugar and a negative globulin reaction. The blood and spinal fluid Wassermann tests were negative.

CASE XII.—M. S. (24,476), aged sixteen days, was a full-term infant, born after a difficult instrumental delivery. He was admitted to the Babies' Hospital with the statement that he had been normal until the tenth day of life when he became drowsy and refused to nurse. Convulsive movements were observed but no definite convulsions. His first lumbar puncture showed 19 cells, 60 per-cent of which were lymphocytes. The test for a reducing substance was positive, as was the globulin test. Six days after admission 264 cells were present, the globulin test was positive and the quantitative sugar determination showed 39 mg. per 100 cc. Ten days after admission the cells had fallen to 87 and the globulin test was negative. Nineteen days after admission the cell count had fallen to 49 cells; the quantitative sugar remained practically the same, that is, 41 mg. per 100 cc. Moderate fever was present for five days. During the period of hospital observation symptoms pointing to mechanical obstruction to breathing were noted for several days. A profuse discharge of pus from the nose was followed by prompt relief of these symptoms. The infant was discharged cured after a month's period of hospital observation.

CASE XIII.—A. C. (24,874), aged twenty-five days, a full-term infant, normal delivery, with a birth weight of 6 pounds and 2 ounces, was admitted to the hospital on account of drowsiness for three days and refusal to nurse for three days. It was also stated that the infant had never cried vigorously, but that he seemed normal until three days prior to admission. The infant was

jaundiced, seemed drowsy and did not cry when disturbed. The first lumbar puncture showed 126 cells, 82 per cent of which were polymorphonuclears; the globulin test was positive as well as the test for sugar. Ten days after admission 70 cells were present. Sixteen days after admission the fluid showed 43 cells with 28 mg. of sugar per 100 cc of fluid with chlorids of 725. On the nineteenth day the fluid showed only 28 cells with a faint globulin reaction and 32 mg. of sugar and 688 of chlorids per 100 cc of fluid. Fever was present for twelve days. The infant was discharged on the thirtieth day cured of the condition for which he was admitted. At eight months of age he was apparently a normal infant.

CASE XIV.—D. C. (private patient, 819), aged four weeks. Normal labor; birth weight, $7\frac{3}{16}$ pounds; cried well at birth. Was normal for first three weeks of life. He then began to refuse to nurse and became drowsy. Three days after onset temperature rose to 103° F. and after a few days gradually subsided to normal. When four weeks of age he was in such poor condition that he was admitted to the hospital. He was transfused and a lumbar puncture was done. The cerebrospinal fluid was clear and showed 135 cells, 74 per cent of which were lymphocytes. A faint globulin reaction was present. The test for sugar was positive. The infant was discharged improved, and for two months after his acute illness his cry remained extremely feeble. At the age of six months he was somewhat backward physically but his mental development was normal.

Four cases are presented for diagnosis, all under one month of age. All had increased cell counts and positive globulin reactions. Three of the 4 showed diminished sugar in their spinal fluid. All were cured of the meningeal condition for which they were admitted to the hospital.

The following case differs greatly in symptomatology from the first three cases.

CASE XV.—P. P. (private patient), aged five weeks, was born after an easy labor, although low forceps were applied. The weight at birth was 7 pounds. The infant thrived during the first month of life, nursed well and gained normally in weight, but the mother was impressed with the type of cry, which to her never seemed vigorous. At the beginning of the fifth week the infant had a "cold." Fever was noted. He looked acutely ill, refused to nurse and showed weakness of the right arm. Examination revealed an apathetic infant with paralysis of the right arm and leg and paralysis of the right half of the abdominal wall, which showed distinct ballooning. Retention of urine was present. There was dilatation of the right pupil. The cry was extremely weak. The knee jerk was

diminished on the affected side; the day following it was absent and has remained so to date. A clonus was present on the affected side. The knee jerk was exaggerated on the left side. There was no bulging of the fontanel at any time. The routine laboratory tests, including blood, urine and Wassermann of blood and cerebrospinal fluid, were negative. Roentgen-ray showed the vertebral column apparently normal. Lumbar puncture showed 90 cells, 54 per cent of which were polymorphonuclears. The globulin test was strongly positive. Two days later the cells were reduced to 40, with a predominance of lymphocytes and a globulin test which was strongly positive. The infant is now four and a half months of age, well nourished and vigorous, but the arm and leg show spastic paralysis. The bladder symptoms and paralysis of the abdominal muscles disappeared a few days after they were first noted. The right pupil is still slightly larger than the left. Some improvement in muscle power has been noted in the upper arm and shoulder.

CASE XVI.—M. M. (24,532), admitted at the age of three days, is offered as a typical case of meningitis in the newborn caused by pyogenic organisms, in contrast with the cases just described. She had been a normal infant for the first two days of life. Convulsions began on the third day and a vaginal discharge and swelling of the right lower extremity was noted. A lumbar puncture showed 200 cells with yellow fluid, a negative sugar reaction and a strongly positive globulin test. *Streptococcus hemolyticus* was obtained from the umbilicus, the blood and the spinal fluid. Culture from the vaginal exudate showed *Klebs-Loeffler bacilli*. The infant died on the day of admission, and at autopsy a purulent leptomeningitis was observed in addition to diphtheria of the vulva.

Bronchopneumonia. The cerebrospinal fluid of 20 infants was examined in which the primary diagnosis was pneumonia. The majority of these cases were bronchopneumonia, many with complicating infections. The youngest case was twenty-eight days of age and the oldest was five years. Lumbar punctures were done in these cases because of symptoms which suggested the possibility of a central nervous lesion. Of the 20 cases, 9 died.

In every case the fluid obtained was clear and colorless, in 4 cases the test for globulin was positive, in 2 instances it was questionable and in 12 cases it was negative. The qualitative test for a reducing substance was positive in all the cases. In specimens of cerebrospinal fluid from several patients no cells could be found. The highest cell counts were 10, 12 and 10 and 11 respectively, and the average count for the 20 cases was 4 cells. The 4 cases with the highest cell counts died of pneumonia, the condition for which they were admitted to the hospital.

A quantitative sugar determination was done in 13 of the cases,

and in all it was within the range of normal, that is, between 45 and 85 mg. per 100 cc. The average for the 13 cases was 67 mg. per 100 cc, which might be taken as a normal for infants and young children. The lowest amount found was 47 mg., and the highest was 83 mg.

A qualitative determination of chlorids was done in 13 cases. These varied between 638 and 738 mg. per 100 cc, which is within the normal range, that is, 600 and 750.

Of interest is the fact that in these 20 cases, all of which had either one or more of such symptoms as irritability, rigidity of neck, vomiting, drowsiness, coma or convulsions, which led to the suspicion that the central nervous system might be invaded, yet not one had very marked increase in the number of cells nor had any of the group a marked change in the amount of dextrose. The only finding which could be termed pathological was a positive globulin reaction in 4 of 20 cases, which, in our opinion, was possibly due to the presence of a few red blood cells incident to the trauma produced by puncture. This is a commentary both as to the frequency of such symptoms in pneumococcic infections and the unreliability of the clinical signs of central nervous involvement in this type of infection.

Disturbance of the Digestive System. In this group of 10 cases are placed such conditions as dysentery, acute intestinal indigestion and intoxication. The youngest patient was four months of age and the oldest eight years. The average age was twenty-three and three-tenth months. In every instance the fluid was clear and colorless. In 8 cases in which a test for globulin was done it was positive in 3 cases and negative in 5 cases. The qualitative test for sugar was positive in all the cases. In 2 of the cases no cells could be found in the cerebrospinal fluid, and only 1 case in which 15 cells were found showed any appreciable cellular reaction.

A quantitative sugar determination was made one or more times in 8 of the cases. On the whole, this group showed a higher per cent of dextrose than the pneumonia group. The lowest showed 53 mg. per 100 cc and the highest 140. The average for nine estimations was 97 mg. per 100 cc as compared with 67 mg. for the first named group.

Several factors may have operated to cause this increase in sugar. Diarrheal cases admitted to an infant's hospital usually show a marked degree of dehydration as a result of frequent watery stools. In consequence, all of the body fluids, including the cerebrospinal fluid, would show varying degrees of concentration sufficient in many cases to increase the percentage of dextrose. In other cases treatment for dehydration with frequent injections of fluid under the skin, intraperitoneally, etc., might for a brief interval induce a saturation of the body tissues with fluid, and in conse-

quence a relative diminution of the solids, such as sugar, might occur. Many of these dehydrated infants are treated with hypodermoclyses of dextrose solution, varying in concentration from 3 to 6 per cent. The introduction into the body of 15 to 30 gm. of dextrose in the course of a few hours has been shown to raise the sugar value in the cerebrospinal fluid.

The chief interest from a clinical standpoint is the high percentage of sugar in some of the cases in this group, especially among those in which drowsiness or stupor occurred.

CASE XVII.—Of interest is E. M. (23,532), who, during two attacks of diarrhea at intervals of a year, presented symptoms which pointed to involvement of the central nervous system. The patient was admitted at the age of fourteen months because of vomiting and convulsions. Lumbar puncture revealed clear fluid with 15 cells, all of which were lymphocytes. The test for a reducing substance was positive. She was discharged cured, with the diagnosis of acute intestinal intoxication. She was readmitted at twenty-six months of age because of vomiting, drowsiness and convulsions. Lumbar puncture revealed only 4 cells, with a positive reaction for a reducing substance. The quantitative test for sugar showed 78 mg. per 100 cc and 700 mg. of chlorids. The blood Wassermann was negative. She was discharged cured, with the same diagnosis as on the previous admission.

This is a striking commentary on the tendency shown by certain children to manifest symptoms pointing to disturbance of the central nervous system in the presence of fever, whether due to infection or to chemical disturbance. In infancy the most common nervous symptoms are vomiting, irregular respiration, exaggeration of the reflexes, irritability, drowsiness, stupor and convulsions. In childhood the commoner symptoms are restlessness, as manifested by picking at the bed clothes, tossing about in bed, delirium, muscular tremor and coma. Some inherent defect in nervous tissue may possibly explain why certain children are prone to such symptoms in the presence of fever while others escape them altogether.

Status Lymphaticus. Three cases of status lymphaticus were demonstrated at autopsy in which lumbar punctures had been done during life. The ages were twenty-two months, sixteen months and five weeks respectively. In all 3 cases the cerebrospinal fluid was clear and colorless. The cell count showed 4, 6 and 25 cells respectively on the first lumbar puncture after admission to hospital. The reaction for a reducing substance was positive in all, and the globulin test was positive in 2. The quantitative sugar determination was well below the normal limits in 2 of the cases and normal in 1 case. The chlorids were normal in all 3 cases.

CASE XVIII.—P. F. (24,242) was admitted to the hospital at the age of five weeks because of irritability, rigidity of the neck and drowsiness. The diagnosis during life was sepsis. At the first lumbar puncture clear fluid was withdrawn which showed 25 cells, 60 per cent of which were polymorphonuclears. The test for a reducing substance was positive, and the test for globulin, which was only done on the fluid removed at the first puncture, was negative. Chemical analysis gave 33 mg. of sugar per 100 cc of fluid and 725 mg. of chlorids. A subsequent lumbar puncture showed a turbid fluid with 70 cells per cm., 71 mg. of sugar and 675 mg. of chlorids. A culture of the blood showed no growth. At autopsy a hyperplastic thymus weighing 30 gm. and an acute splenic tumor weighing 23 gm. were noted in addition to an hypertrophy of the pituitary. It seemed likely that the infant's death had been hastened by the lymphatic state.

Cerebral Hemorrhage Occurring at Birth. The diagnosis of cerebral or cord hemorrhage can be made but rarely on lumbar puncture alone. Trauma produced by the needle frequently releases blood into the spinal canal. This is of such common occurrence in early infancy, even when performed with the greatest skill, that it invalidates the diagnosis of cerebral hemorrhage, if made on the presence of a few red blood cells or a large amount of blood in the cerebrospinal fluid obtained by lumbar puncture. If, however, bloody fluid is obtained at the first lumbar puncture performed in the first few days of life and successive punctures show a gradual diminution in the amount of blood, and eventually clear fluid is obtained, it may be held that cerebral hemorrhage has occurred.

If blood stained fluid is obtained by lumbar puncture in early infancy, and a yellow color does not disappear on standing or after centrifuging, it may be accepted as diagnostic of cerebral birth hemorrhage, because the xanthochromia is the result of hemolysis.

The presence of bloody cerebrospinal fluid caused by cerebral hemorrhage at birth tends to disappear rapidly, and unless the hemorrhage has continued it will disappear entirely, usually by the end of the second week of life.

Such manifestations of cerebral hemorrhage as drowsiness, feeble respiration, feeble cry, refusal to nurse and a gray color of the skin, with or without convulsions or a bulging fontanel, are of greater significance to the clinician than the presence of a few red blood cells which may have resulted from trauma.

In the following group of cases lumbar puncture was done to exclude the possibility that an infection of the central nervous system might have been the cause of such symptoms as irritability, rigidity of the neck, exaggerated reflexes, convulsions, etc. Many of the infants were too old to consider the examination of cerebrospinal fluid as an aid in the diagnosis of cerebral hemorrhage due

to birth trauma. The diagnosis on discharge was made on the history of a difficult labor, the condition of the infant during the first few days of life plus the usual residual physical findings, supposedly denoting birth hemorrhage, which unfortunately are often purely speculative.

Of the 15 cases from two days to twenty-two months of age, with an average age of six months, only 3 showed xanthochromic fluid. These were two days, five days and two months of age respectively. The average cell count for 15 cases was 5.4 cells per c.mm. One of the xanthochromic fluids showed 14 cells per c.mm. and another 20 cells. None of the specimens of cerebrospinal fluid showed an increased cell count. The globulin reaction was positive in 4 of 14 cases, and the test for a reducing substance was positive in the 10 cases in which the reaction was done.

A quantitative test for sugar was done sixteen times in 11 patients; all were practically within normal limits. An infant, aged two days, with xanthochromic fluid showed only 44 mg. of dextrose per 100 cc, which was confirmed on subsequent examination. A quantitative determination of chlorid was made on 11 patients, with sixteen examinations. All were within the range of normal.

Conclusions. 1. In cerebrospinal meningitis the sugar content of the cerebrospinal fluid is diminished in cases with moderately increased cell counts and absent in fluids with high cell counts, particularly purulent fluids. A gradual increase in the sugar was noted coincident with a decrease in the number of cells.

2. In a small group of cases of encephalitis the only uniform finding of diagnostic interest was a sugar content higher than in any other type of case.

3. In 3 cases of encephalitis, due to poisoning by lead, the test for globulin was positive, and in 2 of 3 cases there was pleocytosis.

4. In tuberculous meningitis the cellular reaction seems to bear no relationship to the number of tubercle bacilli in the cerebrospinal fluid.

5. A diminution of dextrose was noted in the cerebrospinal fluid of tuberculous meningitis, which might serve as a help in the early differential diagnosis between this disease and encephalitis.

6. There is little evidence of any diagnostic value in a chlorid determination in tuberculous meningitis, or in any other meningeal or extrameningeal conditions in infancy and early childhood.

7. In a small group of cases of pneumococcus meningitis the dextrose content of the cerebrospinal fluid was similar to the other purulent types of meningitis; that is, consistently low.

8. It was noted in a previous study of a group of cases of congenital syphilis, and again in this group that congenital syphilis may involve the central nervous system without showing an increase in the number of cells in the cerebrospinal fluid.

9. The quantitative estimation of dextrose in the cerebrospinal fluid of congenital syphilis showed it to be present in normal amounts in nearly every instance. In syphilitic meningitis there is a reduction in the amount of dextrose present in the cerebrospinal fluid comparable to the reduction noted in other types of meningitis with high cell counts.

10. In 13 cases of pneumonia the dextrose content of the cerebrospinal fluid was within the range accepted by us as normal. The highest cell counts in 20 cases were 10, 12, 10 and 11 respectively.

11. In a group of cases of disturbance of the digestive system an increased amount of dextrose was found. The results may be explained by the concentration of body fluids due to diarrhea and the introduction into the body of dextrose solution as a therapeutic measure.

12. If a blood stained fluid is obtained by lumbar puncture in the first few weeks of life, and the clear supernatant fluid is yellow, standing or after centrifuging, it may be accepted as evidence of cerebral hemorrhage. The presence of red blood cells in the cerebrospinal fluid obtained by lumbar puncture in the first few weeks of life is not diagnostic of cerebral hemorrhage, since the factor of blood introduced by trauma at the time of puncture cannot be excluded.

EARLY BED-SORES AS A DIAGNOSTIC SIGN OF CARBON MONOXID POISONING.

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CARBON monoxid poisoning is of rather frequent occurrence and any sign that will help in the diagnosis of obscure cases must be of value. It may result from inhalation of illuminating gas, coal-water gas, air vitiated by defective stoves, or the exhaust gases from the motors of automobile or motor boat leaking into a closed space. The danger is the greater because carbon monoxid of itself is a gas without special odor, color, or taste. There are cases on record of fatal poisoning from the gas conducted under ground from a distant location. The finding of an unconscious person, under circumstances leaving in doubt the cause of the coma, should awaken the suspicion of possible carbon monoxid poisoning.

Skin manifestations are not at all uncommon. Erythemas over cheeks and nose, localized edemas, vesicles, herpes, bullæ, red or bluish-red spots on the front of neck, trunk and thighs, purpuras and gangrene of extremities due to carbon monoxid poisoning have been noted. Very little can be found in the literature concerning

local necrosis and gangrene in areas exposed to pressure. It is the belief of the writer that these lesions are fairly common and are either overlooked, thought to be traumatic, or considered to be of no clinical significance.

The resulting carbon monoxid hemoglobin, which arises from the firm union of carbon monoxid with the hemoglobin of the red blood cell, is the primary cause of the clinical and pathological state which develops. This combination does not destroy the hemoglobin but prevents it from taking up oxygen; since the affinity of hemoglobin for carbon monoxid is three hundred times as great as that for oxygen. Straight tissue asphyxia arises because of the lack of tissue respiration. The formation of CO-Hb is evidenced by the cherry-red appearance of the blood during the early stages of asphyxia. Harbitz has shown that differences in susceptibility occur: Men, because of their need of more oxygen; those suffering from gastrointestinal, heart, lung, and exhaustive states are more susceptible and therefore succumb the more readily.

The early coma is due to severe damage to the ganglion cells of the cerebral cortex. If the patient survives the deep coma, a period of stupor followed by retrograde amnesia for events from the first to the fourth day of poisoning ensues. Therefore, the inability of many individuals to account for the cause or duration of their unconscious state. During the state of complete unconsciousness, the patient usually lies on his back, and the areas of skin that are in almost direct contact with the underlying bony structures—such as the prominence of the spine of the scapula near the vertebral border, sacrum, and heels—are markedly pressed upon. It is hardly likely that he would lie for any considerable period of time in the lateral position, in which event one would expect to find the early bed-sores over the elbow, superior spine of the ilium, great trochanter and external malleolus of one side. It is to be expected, that the less resilient the support on which the patient lies, the longer and deeper the coma, the longer a fixed position is maintained, the earlier and surer will these lesions appear. The mental dullness which frequently persists may be a factor in the failure of the patient to call attention to the lesion.

In these squeezed areas, the pressure causes constriction of the bloodvessels with possible secondary thrombosis. Anemic areas result, soon to be followed by atonic hyperemia. As a result of stasis and the diffusion of blood pigment, the area assumes a livid red color, which soon becomes discolored, moist, soft and gangrenous. Ulceration occurs. Healing is apt to be very slow and the areas may become secondarily infected with organisms from the skin or rectum. As with other types of ulceration, secondary bacteriemia and pyemia are possibilities.

The absence of tissue respiration and the continued pressure over certain vulnerable areas explain the early formation, within a few

days, of the bed-sores on the scapular, sacral and heel areas. Other factors may play contributory, though minor roles. (1) Heart weakness as evidenced by small pulse, low blood pressure and circulatory disturbances allows of peripheral stasis which in turn favors bed-sore formation. (2) Weak respiratory movements aid in decreasing circulatory movements and the rate of elimination of carbon monoxid, thus continuing the condition of tissue asphyxia which is so prominent a factor in the causation of this lesion.

Case Reports. **CASE I.**—Michael K. aged fifty years, was brought into the Greenpoint Hospital unconscious January 4, 1925. There was a questionable history of his having been found in a room in which there was an open gas jet. A venesection was done, removing 12 ounces of cherry-red blood. Slight rigidity of the neck, bilateral Kernig, slight left facial weakness, normal pupils, and spastic extremities were revealed on examination. A purpuric area was seen over the vertebral border of each scapula. A similar spot 3 inches in diameter was over the sacrum and there were purpuric areas the size of a half dollar over each heel. These were at first assumed to be bruises. The patient gradually recovered consciousness but his face remained expressionless and he responded sluggishly to questions. He had no recollection of what occurred and could throw no light on either the cause of his coma or the peculiar skin lesions. The Wassermann test of the blood and the blood chemistry were both negative. A spinal tap yielded clear fluid under slightly increased pressure containing 15 red cells and 5 polymorphonuclear leukocytes to the cubic millimeter, negative colloidal gold. The blood count 14,600 white blood cells, 80 per cent polymorphonuclears; 4,192,000 red blood cells. The temperature ranged between 100° and 102° F. for two weeks and gradually became normal. The pulse varied from 90 to 110; the systolic blood pressure was 110. The respiration ranged from 20 to 30. Within forty-eight hours after admission the purpuric spots on the heels and sacrum became definitely necrotic and gradually broke down. At the present writing almost two months later these bed-sores are not yet completely healed, and the patient presents a marked Parkinsonism. In this case because of the indefinite history, the finding of the red blood cells in the spinal fluid, fever, leukocytosis, initial coma and later evidences of meningeal irritation, it was assumed that the patient had sustained a basal meningeal hemorrhage. The early bed-sores were misinterpreted until the observation of identical lesions in the following case enabled us to make the correct diagnosis in retrospect.

CASE II.—John M., aged forty years, was found in bed unconscious. There was a heavy odor of gas in the room. After the use of the pulmotor he was brought to the Greenpoint Hospital

January 26, 1925. He could not be aroused. The pulse was rapid and full; blood pressure 80 systolic, 40 diastolic. Knee-jerks present, no Kernig or Babinski. Respiration 25, temperature 99° F. Less than forty-eight hours after admission the patient was found to have erythematous areas over both scapular regions and sacrum, with purpuric areas and bleb formations over both heels. There was marked cyanosis over the entire body. The day after admission he was semiconscious, face mask-like and his temperature, pulse and respiration gradually rising. Dullness, bronchial breathing and subcrepitant rales were found in right axilla and left posterior chest. Spinal tap yielded clear fluid under slightly increased pressure, 50 red blood cells, 5 lymphocytes and 5 polymorphonuclears to the cubic millimeter; normal Fehling reduction, no globulin increase and negative Wassermann. Blood count 14,400 white blood cells, 80 per cent polymorphonuclears, 4,500,000 red blood cells on second day. The patient died on the fifth day with a temperature of 102° F., pulse rate 120, and respirations 40 before exitus. It was the coincidence of the early bed-sore formation in two patients both in the ward at the same time, one a suspected and the other a definite case of gas poisoning, that called the attention of the writer to this phenomenon and the possibility of it being used as a diagnostic aid.

CASE III.—The writer is informed of a definite case of carbon monoxid poisoning in another hospital in an adult male, who on arousing from coma complaining of sores upon his back which he did not remember having had before the accident.

Conclusion. Carbon monoxid poisoning is attended by a great decrease of tissue respiration. The severely poisoned individual lies on his back for a considerable time and the resulting pressure over the scapular, sacral, and heel areas together with the above factor of tissue asphyxia leads to early bed-sore formation.

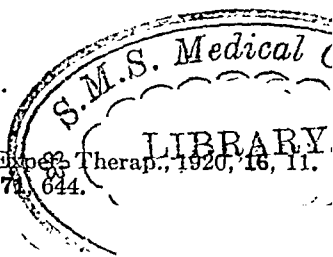
The very early appearance of bed-sores in a previously comatous or still stuporous individual is almost pathognomonic of carbon monoxid poisoning, and is not found as early in other conditions.

This sign is therefore of great value from a clinical and medico-legal viewpoint.

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PRIMARY CARCINOMA OF THE LUNG.

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PRIMARY carcinoma of the lung is considered a rare condition by many writers. We frequently find in the literature such statements as "carcinoma is by far the most frequent form of malignant tumor of the lungs and yet it is absolutely and relatively infrequent;" "cancer of the lung may be primary or secondary, the former is rare, the latter common;" "while primary tumors are rare, secondary growths are not uncommon. Carcinoma is the most common primary form;" "primary carcinoma of the lung is an uncommon disease." However, within a comparatively short time we find the belief growing that this condition is not so rare as commonly supposed. "Increased interest in primary carcinoma of the lung in recent years has furnished statistics which indicate that the condition is more frequent than is usually stated" is a recent comment on the subject. Norris and Landis write, "primary carcinoma of the lung is generally looked upon as of relatively rare occurrence. This belief is not well founded according to Sailer and Torrey." Ewing states that "primary malignant tumors of the lung form about one per cent of all cancers. Secondary growths due to carcinoma are ten times more common than primary growths. Primary growths occur more frequently in males than females in a ratio of 3 to 1, while metastatic growths are more common in females. The chief etiologic factor is tuberculosis. Of Wolf's 31 cases, 13 were associated with tuberculosis. Squamous-cell carcinoma developing in the wall of a tuberculous cavity is described by Schwalbe, Friedländer and Perrone. Wolf found tuberculous lesions throughout diffuse carcinoma or surrounding tumor masses. Oertel points out that the association may be accidental, at other times the two processes exist in symbiosis, while rarely tuberculosis appears to inhibit the carcinoma. Several cases in which there

was active miliary tuberculosis with carcinoma suggest that the malignant process may light up latent tuberculous foci. Rupture of anthracotic nodes into the bronchi is held by Wolf as responsible for some cases of bronchial carcinoma." Other etiologic factors may be chronic bronchitis, chronic fibroid pneumonia and trauma.

The admission of 3 patients with primary carcinoma of the lung to the same ward at Kings County Hospital between February 12, 1924 and June 1, 1924, a period of three and a half months, causes the writer to believe that this condition is more common than is usually believed. Two of the patients were on the writer's service and one, L. H., was on the service of Dr. B. F. Corwin, whose service alternates with the writer's and who has kindly consented to allow a report of the case.

Case Reports. CASE I.—H. K., aged forty-nine years, was admitted to the writer's medical service, Kings County Hospital, February 12, 1924 and died February 24, 1924. His chief complaints were a productive cough with mucopurulent but not blood tinged sputum, which began two months before admission to the hospital; pain, which gradually developed in the left side of the chest, on admission was almost constant and increased on coughing; dyspnea was marked. Cough and pain were severe enough to prevent sleep. The patient had lost 10 pounds during the past two months and had grown progressively weaker. Aphonia was noticed six weeks before admission to the hospital. His associated symptoms were occasional fever, no chills, no sweats, a chronic productive cough, marked dyspnea, no palpitation, no precordial pain. There was occasional swelling of the ankles for the past year, absent in the morning but present when on his feet for some time. He had a fair appetite, no nausea, no vomiting, bowels regular, not medicated. He was easily fatigued, had lost weight, and slept poorly from pain and cough.

Family history shows his mother died of apoplexy, aged fifty-seven years, and his father of typhoid fever at thirty-six years; one brother is alive and well; two sisters died in childhood, cause not known to the patient; no history of tuberculosis or malignancy. Previous personal history: During childhood the patient had very severe attacks of scarlet fever and diphtheria. He also had measles, mumps and whooping cough. The patient states that he was a sickly child. During adult life the only disease was a bilateral, lower lobe, lobar pneumonia two years before admission to Kings County Hospital. There was a negative history for gonorrhea and lues.

Physical examination revealed a moderate framed, poorly-nourished, pale adult complaining of cough, pain in chest and shortness of breath. Head, eyes, nose and ears were negative. There was no glandular enlargement in the neck. Chest examina-

tion showed a narrow, poorly-nourished chest with diminished expansion of both sides. There was marked distention of the superficial veins of the chest. Tactile fremitus was diminished throughout the left chest. There was impaired resonance over both upper and lower lobes posteriorly on the left side, and harsh breathing with numerous loud moist rales throughout the left chest with dry friction rub over left base. The voice sounds were diminished throughout the left side. The abdomen showed no localized areas of tenderness, no palpable masses and no herniæ. The inguinal glands were palpable and shotty.

Abscess or malignancy of the lung or mediastinum was suspected. Roentgen-ray examination showed a neoplasm in the left upper lobe and one in the left lower lobe. A bronchoscopy was performed by Dr. M. C. Myerson who confirmed the diagnosis of malignancy of the lung; his report follows: "Upon entering the left main bronchus with the bronchoscope a very penetrating foul odor was noticeable which was not present before. When the bronchoscope came to a point opposite the upper lobe branch bronchus a viscid milky fluid was encountered. This fluid after evacuation was clearly demonstrated to come from the upper lobe bronchus. A special upper lobe suction tube was easily passed. The bronchoscopic picture confirms the diagnosis. There is no main bronchus pathology but probably some upper lobe branch bronchus pathology which cannot be seen."

During the patient's stay in the hospital the cough was always troublesome. Following the bronchoscopy the patient stated that he expectorated an entirely different type of sputum, having a bad taste and foul odor but raised very much more easily. The reason for this was that the left upper bronchus leading to the tumor was plugged and aspiration through the bronchoscope opened the occluded bronchus making expectoration easier and cough less painful. Five days after bronchoscopy the patient expectorated considerable foul smelling bloody sputum during the afternoon, his pulse became weak and rapid and he showed signs of collapse. At five o'clock the following morning he raised a large quantity of bright red blood and died of hemorrhage. The patient had a fever the first four days in the hospital, the highest point being 102.4° F.; the respirations rose as high as 34 per minute, averaging 26. The laboratory reports gave a normal urine; sputum negative for tubercle bacillus; blood Wassermann negative; blood chemistry normal. Microscopic examination of pus from the bronchus showed an admixture of fibrin, red blood cells and inflammatory cells. No malignant cells were observed.

The findings at autopsy were as follows; only those of positive interest being recorded here:

Anatomic Findings. Necrotic mass in upper lobe of left lung;

chronic pleuritis; petechial hemorrhages of right lung; pericardial effusion; left pleural effusion; perihepatitis; fatty cirrhosis; chronic interstitial splenitis; accessory spleen.

Section. On median incision and removal of the sternum there was found to be present a very small amount of subcutaneous fat. The peritoneal and right pleural cavities are free from fluid. The pericardium is distended and contains about 400 cc of straw-colored fluid. The left pleural cavity is obliterated except for the portion over the lower lobe posteriorly where there is a cavity containing about 600 cc of reddish-brown, foul-smelling fluid.

Right Lung. The right pleura is smooth and glistening, and a few petechial hemorrhages are found on its surface. The lung is moderately hypertrophied, pale and somewhat anthracotic. The lung floats in water, is well aerated and on section appears normal. The pulmonary arteries are empty.

Left Lung. The pleura over the entire lung is thickened. The upper lobe is nearly entirely replaced by a large, broken-down mass surrounded by indurated lung tissue. This tissue is not definitely encapsulated. The lower lung is infiltrated and edematous. The lung sinks in water.

Trachea. The trachea contains a bloody fluid throughout, and there is a large blood clot lodged in its upper portion, nearly occluding the lumen.

Esophagus. Contains bloody fluid throughout.

Peribronchial Glands. The peribronchial glands are not enlarged or calcified, but are the seat of anthracosis.

Heart. The heart weighs 400 gm. "Milk spots" are present on its posterior surface and there is some increase in the epicardial fat. The myocardium is pale but otherwise shows no lesion. The valves show no pathology.

Aorta. The aorta is normal throughout except for a few yellowish plaques in the descending portion.

Cause of Death. Pulmonary hemorrhage.

HISTOLOGIC DATA: *Heart.* Cloudy swelling; hydropic degeneration.

Lungs. Alveolar-cell carcinoma; pulmonary abscess; chronic pleuritis.

Peribronchial Lymph Node. Subacute and chronic hyperplastic lymphadenitis; no evidence of tumor metastases.

Spleen. Edema. *Liver.* Cloudy swelling; chronic perihepatitis.

Adrenals. Normal.

Kidneys. Focal areas of fibroblastic change, but on the whole the kidneys are practically normal. *Pancreas.* Normal. *Aorta.* Atheromatous.

Dr. Hala, pathologist at the Kings County Hospital, has given the following detailed report of the specimen of the left lung:

Gross Description of the Lung. The pleura over the entire lung is thickened. The bronchus is found filled with blood. There is no gross evidence of neoplasm affecting the bronchus. Upon transection of the lung, practically the entire upper lobe consists of a broken down, necrotic material surrounded by a peripheral wall of indurated lung tissue. The lower lobe shows scattering irregular areas, greyish pink in color, of varying size, from 2 mm. to 1.5 cm. in diameter. These areas suggest neoplasm.

Microscopic Examination. Sections show carcinoma in which the predominating type of tumor cell is cuboidal. In general the cells are in compact masses filling up the entire air sac, although occasionally they are found lining the alveolar wall. Numerous "giant" cells occur. Marked areas of necrosis are also outstanding features. Mitoses and amitoses are common. There is very little reticulum in the tumor proper. Focal abscesses are not uncommon. In a few areas, the tumor cells closely compacted assume more or less of a spindle shape.

This neoplasm is evidently derived from alveolar epithelium. It is rather difficult to classify it as either a diffuse carcinoma or multiple nodular carcinoma. The gross appearance of the lower lobe of this lung would seem to point to multiple nodular carcinoma, while the extensive involvement of the upper lobe favors diffuse carcinoma. It is possible, however, that the lesion was not really diffuse in the upper lobe, the predominating histopathology there being abscess formation. This case showed no metastases.

CASE II.—L. H., a Russian, aged fifty-one years, was admitted to the service of Dr. Corwin on March 1, 1924 and died March 31, 1924. The chief complaints on admission were pain in the right chest and back, productive cough and profuse night sweats. This condition had existed to the patient's knowledge for six weeks. The cough was productive of mucopurulent expectoration but no blood. The family history was negative. The patient's previous personal history was negative except for two broken ribs on left side thirteen years before the present illness. The physical examination showed a large-framed, poorly-nourished, white Russian male, clear mentally but unable to speak English. Scalp, eyes, ears and nose were negative. Mouth showed teeth and gums in poor condition. The cervical lymph glands on the right side were enlarged. There was also distention of the superficial veins of the right neck and shoulder. The chest was fairly well formed with prominent clavicles. There was a small nodular tumor over the left pectoral muscle. There were exaggerated breath sounds with areas of bronchovesicular breathing and impaired resonance with mucous rales throughout the lower right chest posteriorly. Heart sounds were regular, rapid and of fair quality. The heart was not enlarged. There were no murmurs present. Blood pressure, 110 systolic,

50 diastolic. The back, abdomen, genitals and extremities were negative. A provisional diagnosis was made of either chronic pulmonary tuberculosis, or mediastinal neoplasm extending into the right lung.

The subcutaneous tumor over the left pectoral was removed for diagnosis shortly after the patient's admission. The pathological report on the biopsy specimen follows: "The specimen consists of a section of a lymph node and a subcutaneous nodule. There is present a tumor composed of closely packed squamous epithelial cells showing both mitotic and amitotic changes. Diagnosis: Squamous celled carcinoma, metastatic."

It was noted that during examinations or during excitement the patient developed an urticarial reaction which was linear in type and appeared on the skin of the arms, chest and abdomen. Sixteen days after admission many subcutaneous nodules appeared over the body and extremities, and increased rapidly in number.

The report of a bronchoscopic examination by Dr. Myerson follows: "The trachea at about the fifth ring down to the middle of the right main bronchus shows a considerable dilatation on the right side posteriorly, with some right side displacement. The right main bronchus from $\frac{1}{2}$ inch from the beginning as far as could be seen to the lower branch shows an irregular papillation of the mucous membrane."

Roentgen-ray of the chest showed a large irregular mass involving the middle and lower lobes of the right lung, pulling the trachea and heart to the right side. There was increased width and density of the mediastinal shadow. The left lung was clear. There was no fluid present. The laboratory reports showed a normal urine. Phenolsulphonephthalein test—37 per cent; 25 per cent; 12 per cent; total, three hours, 74 per cent. The sputum was negative for tubercle bacillus. The blood Wassermann was negative. Blood count and blood chemistry were normal. The temperature varied between 100° F. and 103° F. rectally. The pulse varied between 80 and 130 per minute. The respirations varied between 24 and 40 per minute.

The patient died one month after admission with signs of pulmonary edema.

The autopsy report follows:

Anatomic Findings. Primary carcinoma of the right bronchus; metastatic carcinoma throughout the body; pleural effusion (right); pericardial effusion; old healed scars; edema of the brain; chronic adhesive pleuritis, right; chronic passive congestion of the liver.

Inspection. It is the body of an emaciated, male, white, aged fifty-one years, weighing 150 pounds, and about 5 feet, 8 inches tall. Slight rigor mortis in present with postmortum lividity over the dependent parts. There is a small operative scar just above the sternal end of the clavicle on the right side about 2 inches long and

bears the marks of three sutures. There is an old healed scar about 1 inch long just below the midpart of the left clavicle. Over the entire body with the exception of the face, palms of the hands, soles of the feet, and the scalp, are seen subcutaneous tumors which vary in size from that of a pea to that of a walnut. On section these tumors are found to be adherent to the surrounding tissues and the deeper layers of the skin.

Section. On median incision, very little subcutaneous fat is found. The sternum is removed, the left pleural cavity and the peritoneal cavity are free from fluid. The right pleural cavity contains about 1800 cc of light brown fluid which solidifies on standing into a gelatin-like mass. The pericardium is distended with about 350 cc of light greenish-yellow fluid containing flakes of fibrin. The pleura, pericardium and peritoneum are smooth and glistening throughout.

Head. On reflecting the scalp and removing the calvarium, the brain is found to show some edema of the subarachnoid tissues. It is somewhat congested. On section no pathology is found.

Neck. The deep and superficial lymph nodes are enlarged and indurated. The peritracheal nodes are infiltrated.

Trachea. Appears normal throughout.

Lungs. The left lung well aërated and on section shows no pathology except a few small tumors at the base. The right lung lower lobe is adherent to the diaphragm posteriorly by a dense infiltrated band of tissue. The upper lobe is soft and crepitates, on section it appears normal. The middle and lower lobes are firm and feel indurated. On section these are found to be almost completely replaced by a neoplasm. The lumen of the bronchus just below the bifurcation of the trachea is nearly occluded by new growth which appears to arise from the epithelial lining.

Mediastinum. The neoplasm of the right lung extends into the tissues of the mediastinum, displacing the contents of that space to the left. The peribronchial and all of the lymph nodes of the mediastinum appear to be infiltrated with new growth. There is a large node about the size of a walnut between the trachea and the esophagus about 1 inch above the bifurcation. The trachea and the esophagus appear normal.

Heart. There is a small tumor nodule at the base anteriorly on the epicardium. Aside from this the organ appears normal.

Aorta. Appears normal throughout.

Vena Cava. At the bifurcation of the vena cava attached to its posterior wall and extending about 1 inch into the right common iliac and $\frac{1}{2}$ inch into the left common iliac; there is a small mass of tissue resembling tumor tissue. It is freely movable and apparently has only one point of attachment.

Stomach. Moderately distended with mucus and undigested food. There is a peristaltic constriction at its middle. The mucosa appears normal. The rugæ are prominent.

Intestines. Duodenum and the jejunum appear normal. The mesentery is studded throughout with small pea-sized tumor nodules. At the midportion of the ileum are found two small tumor nodules at the mesenteric attachment and apparently invading the wall of the gut. The appendix is normal except for a small tumor nodule in the serosa. The colon and rectum are free from pathology.

Liver. Normal size; on section shows evidence of chronic passive congestion. The gall bladder is normally distended with bile stained fluid. At its fundus there is a small tumor nodule protruding to the inside.

Spleen. Mottled on section, otherwise normal.

Pancreas. Normal; peripancreatic tissues are invaded with small tumor nodules.

Kidneys. The kidneys show no gross pathology; there is a tumor mass at the upper pole of the right kidney which is pressing on the adrenal. There are a few small nodules in the perirenal tissue of the left kidney; the adrenals, ureters, bladder, prostate and testicle appear normal.

Cause of Death. Primary carcinoma of the right bronchus with metastases throughout the body.

HISTOLOGIC DATA: *Heart.* Adiposis epicardii; metastatic carcinoma of epicardium; cloudy swelling of myocardium.

Bronchus. Primary squamous-cell carcinoma of bronchus.

Lungs. Squamous-cell carcinoma, the tumor showing in places marked degenerative changes.

Peribronchial Node. Metastatic carcinoma.

Liver. Chronic passive congestion; cloudy swelling.

Gall Bladder. Metastatic carcinoma.

Spleen. Chronic passive congestion; edema; atrophy of follicles.

Pancreas. Moderate adiposis; metastatic carcinoma of peripancreatic lymph nodes.

Adrenals. Metastatic carcinoma of periadrenal tissues. *Kidneys.* Metastatic carcinoma. *Appendix.* Metastatic carcinoma of mesoappendix. *Prostate.* Numerous corpora amylacea, otherwise normal.

Intestine. Metastatic carcinoma of ileum, situated in the subserous and serous coats. *Mesenteric Lymph Node.* Metastatic carcinoma.

Skin. Subcutaneous metastatic carcinoma. *Subcutaneous Node.* Metastatic carcinoma. *Brain.* Moderate congestion; edema.

Dr. Hala has given the following detailed report of the specimen of right lung:

Gross Description. The trachea appears normal throughout. The lower lobe of the right lung is adherent to the diaphragm. The upper lobe is soft and crepitant. The middle and lower lobes are firm and feel indurated. The lumen of the right bronchus

just below the bifurcation of the trachea is found almost occluded by a mass springing from the mucosa. Transection through the bronchus and bisecting the entire lung reveals the following pathologic picture: The upper lobe is moderately edematous but otherwise negative. The middle and lower lobes show large and small metastatic masses. The mass observed in the right bronchus extends through the wall inferiorly and invades the surrounding lung tissue. The mediastinal lymph nodes are enormously enlarged and apparently the seat of tumor metastases.



FIG. 1.—Photograph of gross specimen of lung of patient, L. H.
Primary carcinoma of lung.

Microscopic Examination. Bronchus: For a considerable area the normal columnar ciliated epithelial lining is replaced by a heaped-up mass of squamous and large round epithelia, comprising a neoplastic process which is found invading the entire bronchial wall and growing out into the adjacent lung tissue. Lung: Several sections taken through the nodular masses observed grossly disclose a neoplastic process, similar structurally to that observed in the bronchial wall. The tumor shows no tendency to acanthomatous metaplasia, the type of tumor cell remaining the same wherever encountered.

Dr. Hala gave the following opinion: In this case we are dealing with a primary carcinoma of the lung, the original focus of which was the lining epithelium of the bronchus. It is a squamous-celled tumor. The outstanding features were the numerous metastases occurring as they did, into peribronchial and mediastinal nodes, into epicardium, gall bladder, peripancreatic nodes, periadrenal tissue, kidneys, mesoappendix, small intestines (ileum), mesenteric nodes and subcutaneous tissue in various parts of the body. In all these metastases, the tumor has faithfully preserved its original structure.

CASE III.—H. N., male, aged forty-nine years, was admitted to the writer's medical ward, Kings County Hospital, May 28, 1924, and remained until August 3, 1924, when he felt strong enough to return home. He remained at home until September 23, returning in poor condition and died September 30, 1924. His chief complaint on the first admission was weakness, loss of weight, and pain in the right chest. Patient stated that one year before admission, he had a cough with marked dyspnea which improved under treatment. The present illness began seven weeks before admission as a so-called bronchitis, with piercing pain in the right lower chest. This pain became worse on exertion. Dyspnea was marked. At another hospital where he was a patient until one week before admission he had a thoracentesis performed, with a dry tap, and a bronchoscopic examination by Dr. Myerson, with the finding that, the entire right main bronchus was occluded by a neoplasm extending to the bifurcation of the trachea. A specimen was removed which showed a field indicative of epithelial malignancy. He became gradually weaker at the other hospital. On admission we found a poorly-developed and emaciated male complaining of weakness, and pain in right side of the chest. The chest expansion was fair and limited on the right side. Tactile fremitus was diminished on the right side. There was flatness over the right chest with distant bronchial and bronchovesicular breathing over this side in several areas. There were diminished voice sounds over some areas, while in other places the voice sounds were increased. Occasional rales were heard. The heart was displaced slightly to the left.

There was slight, occasional cough and no dyspnea, the pain gradually diminished. During the latter part of June the patient was comfortable, had no complaints, seemed to be gaining weight, felt stronger and was allowed to sit up a few hours each day. On August 2, he was discharged at his own request as he felt stronger, had slight cough, no pain or dyspnea. He promised to return when he needed hospital care.

The sputum was negative for tubercle bacillus. Sputum examination for carcinoma cells showed an admixture of pus cells, fibrin

and elastic tissue fibers. Occasional squamous epithelia of normal appearance or undergoing degeneration were observed but no cells suggesting neoplasm were present.

The urine was normal; the phenolsulphonephthalein output was 22 per cent, 20 per cent, 10 per cent, total in three hours 52 per cent. The blood Wassermann was negative and blood chemistry normal. On May 31, 1924 the blood count was: Red cells 4,032,000; leukocytes 31,900; 81 per cent polymorphonuclears; 16 small mononuclears; 3 large mononuclears; 80 per cent hemoglobin. The temperature was normal notwithstanding the white cell count. Blood examination on June 6, 1924 showed red blood cells 4,480,000; white blood cells 13,700; 67 per cent polymorphonuclears; 18 small mononuclears; 9 large mononuclears; 2 transitionals; 4 eosinophiles; 75 per cent hemoglobin.

The patient returned to the hospital September 23, 1924, with the report that he had done well until two days before admission. At this time he had a very profuse foul-smelling expectoration, marked engorgement of the superficial veins of the chest, neck and head and marked edema of the right side of face. He complained of severe pain in the right chest and extreme dyspnea. The patient died one week after return to hospital.

Blood examination on September 24 showed: Red blood cells 3,840,000; white blood cells 8,700; 78 per cent polymorphonuclears; 13 small mononuclears; 7 large mononuclears, 2 transitionals; 60 per cent hemoglobin. The sputum showed no cells suggestive of malignancy. The autopsy findings follow:

Anatomic Findings. General anemia. Edema of the right upper extremity, right side of face and both feet. Chronic adhesive pleuritis, right side. Hydrothorax, left. Acute fibrinous pericarditis with effusion. Carcinoma of the right lung with necrosis and "abscess" cavity formation. Ulceration of right bronchus. Metastatic carcinoma of peribronchial and mediastinal nodes. Chronic parenchymatous nephritis. Atheroma of the aorta.

Section. On median section of the body there is a marked diminution of the subcutaneous fat which has an anemic, light lemon color. On exposing the thorax there is marked edema of the tissues of the anterior mediastinum. The right pleural cavity is entirely obliterated by adhesions. The left pleural cavity contains about 500 cc of serous fluid. The pericardial sac bulges and on incision is found to contain about 150 cc of straw-colored fluid, in which float flakes of fibrin.

Lungs, Heart and Trachea. The lungs, heart and trachea are removed *en masse*. The entire trachea and bronchi are opened up from behind; situated just below the bifurcation and affecting the right bronchus is a large opening which communicates with a large "abscess" cavity in the right lung, approximately the size of a fist. On transection of the right lung, the entire lung is studded with

irregular, wavy and somewhat circular areas of yellowish color which grossly are not unlike areas of caseation. The peribronchial and mediastinal glands, both anteriorly and posteriorly are matted together in one nodular mass. In some portions the mass is yellowish in color and suggests a caseous process. In other areas, it is slightly grayish in color, firmer and suggests new growth. The inner surface of the pericardial sac is granular and the seat of acute fibrinous inflammation. The epicardium throughout is markedly granular and also the seat of fibrinous inflammation.

Cause of Death. Carcinoma of right lung.

HISTOLOGIC DATA: *Left Lung.* Emphysema. Moderate congestion and edema. *Pericardium.* Acute exudative pericarditis.

Bronchus and Esophagus. Squamous-cell carcinoma of the bronchus infiltrating into peribronchial tissues and beginning to invade the esophageal wall. In one area the growth has extended to the mucosa of the esophagus. The mucosa of the bronchus is entirely necrotic.

Right Lung. Squamous-cell carcinoma. Multiple interstitial and bronchiectatic abscesses. Subacute and chronic pleuritis. Areas of necrosis.

Mediastinal Lymph Nodes. Metastatic squamous-cell carcinoma showing areas of keratinization. Areas of coagulation necrosis.

Pancreas. Moderate lipomatosis.

Liver. Moderate chronic passive congestion. Parenchymatous degeneration.

Spleen. Early chronic interstitial splenitis.

Kidneys. Edema; early chronic glomerulonephritis.

Dr. Hala has given the following detailed report of the specimen of right lung:

Gross Description. The lungs, heart, trachea and esophagus are removed *en masse*. Examination of the esophagus discloses no gross pathology. Upon opening the trachea and bronchi, a large opening is discovered in the right bronchus, just below the bifurcation of the trachea. This opening is found to communicate with what is evidently a large "abscess" cavity occupying the upper lobe of the right lung. This cavity is filled with necrotic, foul-smelling debris of distinctly yellowish color. Scattered throughout the rest of the lung are numerous, irregular, wavy or circular areas averaging $\frac{1}{2}$ cm. in diameter, yellowish in color and not unlike areas of caseation. The peribronchial and mediastinal nodes are enlarged, more or less matted together in one nodular mass. Upon section they are all yellowish in color and suggest caseous tuberculosis. Stains for acid-fast bacilli are negative. A tentative gross diagnosis of caseous tuberculosis, or possible necrosing carcinoma of the lung is made.

The left lung on section is normal.

Microscopic Examination. The mucosa of the bronchus is entirely necrotic. Beneath the necrotic debris, a neoplasm composed of masses of squamous epithelia, often arranged in stratified formation and simulating epidermis, is found invading the entire bronchial wall. Some normal submucous glands are still extant in the submucous coat. The new growth in one area has invaded the esophageal wall and infiltrated toward its lumen at one small, almost microscopic area, replacing the normal mucosa of the esophagus.



FIG. 2.—Photograph of gross specimen of lung of patient, H. N.
Primary carcinoma of lung.

Lung Sections. In the lung, the neoplasm takes on a rather bizarre structure. In some areas the tumor cells line the air sacs with a single layer of rather large polyhedral cells, in other areas by palisaded layers of squamous cells. There is considerable fibrosis between these open air sacs. Such sections give the tumor a pseudo-adenomatous structure. In other sections the tumor retains its original form, that is, acanthoma. Marked areas of necrosis and

abscess formation are common, particularly bronchiectatic abscess. The same structure of acanthoma is retained in the metastases to the mediastinal nodes.

Comments by Dr. Hala upon this specimen follow: This case presents two possibilities. First, it may be a case of primary acanthoma of the esophagus with secondary involvement of the right bronchus and lung, or second, it may be a primary acanthoma of right bronchus with secondary involvement of the esophagus and lung. Against the first supposition is the fact that no gross evidence of tumor was observed in the esophageal lumen at the time of autopsy, nor did the patient ever display any signs or symptoms referable to this tract. Again it would be uncommon for a primary esophageal carcinoma to remain of microscopic size for any length of time. Favoring the second supposition is the fact that primary acanthoma of the bronchus has occurred: cases are cited by Wolf. Moreover, the gross pathology pointed to primary involvement of the bronchus, and the clinical symptoms and signs displayed by the patient were all referable to the bronchopulmonary tract. The curious feature of the case was the gross similarity to caseous tuberculosis.

Limiting cases to neoplasms arising either from bronchi or lung parenchyma, histogenetically three types of carcinoma occur:

1. Neoplasms originating from bronchial epithelium.
2. Neoplasms originating from bronchial mucous glands.
3. Neoplasms originating from alveolar epithelium.

Histologically, carcinomata arising from the bronchial epithelium are either squamous-cell or cylindrical-cell tumors. Among the squamous-cell types acanthomas have been described. Carcinoma arising from bronchial mucous glands is mainly adenomatous in structure, although atypical alveolar types also occur. Carcinoma arising from pulmonary alveoli structurally consists of cuboidal, cylindrical or flat cells, partially or completely filling up the air spaces.

Malignant growths may occur at any age. Up to the middle period of life they are almost invariably sarcoma; beyond middle life carcinoma is more frequent. In these cases we have one alveolar-cell carcinoma, and two arising from the bronchus.

Primary malignant growth may occur as a single large tumor, having its origin in the root of the lung and extending into the pulmonary tissue, or there may be a number of small nodules varying in size from a hazel nut to a small orange. Less commonly the lung may be studded with small nodules resembling miliary tubercles. This widespread distribution, sometimes referred to as carcinomatosis, is seen more frequently as a result of metastasis. The carcinomatous growths are of a white, grayish or grayish-yellow color and are of firm consistency. When they occur in the lung tissue, they are apt to be softer, and may break down and empty

into a bronchus, thus forming a cavity. Metastases to other parts of the body may take place and entirely mask the pulmonary lesion. Metastases to the brain are not an uncommon occurrence in tumor originating in the bronchi.

The symptoms and course of pulmonary carcinoma vary extremely, according to the type of the tumor and the conditions which have led to its development. A large number of cases have been regarded clinically as acute or chronic phthisis, and since tuberculosis is often present without bacilli in the sputum, a differential diagnosis may be impossible. An apparently sudden onset is often due to acute changes in a long-existent tumor. A long history of bronchitis with or without hemoptysis has preceded the discovery of bronchial tumors. The uncomplicated bronchial tumor usually gives physical signs of a progressive intrathoracic growth with cough, hemoptysis, pain, recurring pleural effusion, serous or bloody, dyspnea and cyanosis. About half the cases are of the pleuritic type. Extensive infiltration of the pleura with adhesions may prevent effusion. Fever must be referred to complications. Constitutional symptoms are the same as those of malignant growths in any portion of the body. The acuteness of the disease depends to a large extent upon the rapidity of development of the growth and upon the amount and location of the pressure it exerts. The onset is usually insidious with a gradual failure of health.

The cardinal symptoms of pulmonary growths are: (1) Pain; (2) dyspnea; (3) cough; (4) profuse expectoration; (5) fever from surrounding tissue involvement; (6) pleural effusion; (7) weakness. Not all of these symptoms are present in each case; our second case had no dyspnea notwithstanding extensive involvement and metastases. The presence of blood in the sputum or the occurrence of small hemoptyses is extremely common when the parenchyma is involved. Occasionally the expectorated blood is thick, dark in color, and closely resembles currant jelly; when present, it is highly suggestive of malignant disease. Symptoms referable to the blood vessels are not unusual, and, as a rule, the veins are more frequently affected than the arteries. As the result of pressure on the superior vena cava or one of its main tributaries, the veins over the upper part of the chest may become greatly dilated, varicose and tortuous. In addition the face, upper part of the thorax and arms may become cyanosed, swollen and edematous. The evidences of venous stasis may be limited to one side or may involve both sides. Cachexia is slight in uncomplicated cases. Terminal states are often marked by suppuration, pneumonia and gangrene. The duration of this condition has varied from ten days to four years. A fatal hemoptysis may be the only symptom. The immediate causes of death may be asthenia, hemorrhage, thrombosis, acute infections, pulmonary edema and asphyxia.

Roentgenography will not demonstrate primary malignant

growths in the lungs or bronchi early enough to be benefited by radical chest surgery. Bronchoscopy not only yields the information derived from a clear view of the growth itself, but also will permit the removal of a specimen for histologic examination. Myerson, who bronchosoped each of these patients, writes in a personal communication: "From the viewpoint of early diagnosis, there is no one single procedure of as much value in carcinoma of the lung as bronchoscopy. The importance of this diagnostic procedure is increased by the fact that a majority of pulmonary malignancies originate in the bronchial tree. The exact proportion is difficult to state. When seen by the bronchoscopist, the average case has so extensive an involvement that surgery is out of the question. Radical removal is the only hope for these cases, early diagnosis is essential, and the bronchoscope is the most valuable agency available for early diagnosis."

The writer feels that he has been unusually fortunate in having under observation these somewhat-unusual cases and has given the findings in detail. He wishes to take this opportunity to thank Dr. Hala, Dr. Myerson and Dr. Chapman, house physician, for the assistance they have rendered.

Summary. Primary carcinoma of the lung occurs more frequently than is usually believed. This condition does not cause marked symptoms early in the disease, nor do these symptoms differ greatly from those of pulmonary tuberculosis. The physical findings in these cases, however, are unilateral, thus differing from advanced pulmonary tuberculosis. It is necessary in order to discover this condition early that we should watch more closely: (1) Those patients who complain of persistent cough without demonstrable cause; (2) those who expectorate bloody sputum at intervals with no tubercle ever found in the sputum, and (3) those who complain of general weakness, loss of weight and do not react to the usual methods of treatment. Roentgenography does not aid in the early diagnosis of malignancy of the lungs or the bronchi. Bronchoscopic examination furnishes us with information of these conditions comparatively early and should be advised where indicated. The value of postmortem examinations, so frequently refused, is demonstrated in these cases.

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BLOOD TRANSFUSION: ITS DANGERS AND LIMITED VALUE.

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TRANSFUSION of blood is by no means a new procedure; its early history, going back many ages, has been described quite fully by Dutton.¹

An epidemic of transfusion passed over the profession from 1863 to 1884, during which years many enthusiasts thought it a cure-all for practically everything. von Bergmann, in 1884, published an important work on this subject, and practically put an end to the epidemic. The French Government finally took a hand in the matter and forbade the procedure until the Faculty of Medicine should give its approval, but such approval was never given. (Ravdin.²)

During the last few years what would seem to be another epidemic of blood transfusion has been passing over the country; but, thanks to the recognition of the differences in bloods and the possibilities of their typing, the death record has been much less pronounced, though still, if all unfortunate results were reported, it would doubtless be surprisingly large. Few physicians seem to know anything about the epidemic referred to above, and almost none seem to remember anything about the investigations made by Cullen, of the Johns Hopkins Hospital, referred to later. It would seem very wise, therefore, at this time to make an investigation of the present status of transfusion in an attempt to determine its real value, its dangers and its abuses. Recent literature should be reviewed and surgical opinion sought.

Peterson,³ of New York, in discussing the value and limitations of blood transfusion, especially commends it in anemias following acute or chronic hemorrhages, and also in hemophilia, particularly perhaps in the newborn. He speaks favorably, but not enthusiastically, of its use in purpura and in what he calls hemorrhagic diseases in which he includes hemorrhage seen in icterus, sepsis, nephritis,

and so forth. He confesses disappointment in transfusion in septic conditions, in which, except for its transient stimulating and strengthening action, it seems to have little effect. Transfusion in diabetes, uremia and hyperthyroidism, he says, is practically valueless. He does not accept the theory of Crile as to its use. He says: "Many attempts on my part to influence the course of acute septicemia or bacteriemia by blood transfusion have proven futile." As to the method, he prefers the syringe-cannula or the syringe-stopcock-cannula as approaching more closely the vessel-to-vessel method.

In the discussion which followed the reading of this paper Lewisohn³ expressed himself as heartily in accord with the writer as to the value and limitations of transfusion, but spoke highly of the citrate method of transfusion.

Heyd³ considered transfusion as distinctly not indicated in cases of sepsis, and expressed regret that relatives frequently had exaggerated ideas of the value of transfusion in these cases. In regard to its use in acute sepsis he adds: "There is a very large financial and social aspect in the prevalent idea that blood transfusion should be used in all cases of acute sepsis. It only entails expense to the family, and does not in any appreciable way benefit the condition."

In closing the discussion, Peterson called attention to the dangers of transfusion and the sequelæ. He objected to its use in hopeless cases after other methods have failed, simply in the hope that it might be of benefit. "A procedure," he says, "which lends itself so readily to commercial exploitation is apt to come in for a certain amount of abuse."

In discussing pernicious anemia and transfusion Richard Cabot⁴ speaks as follows: "I do not myself believe that the modern habit of treating it with transfusion prolongs life. It will improve the condition for a certain period of weeks. If we want to have a patient perform some particular act, or see some particular person coming from a distance, it is exactly the right thing to do. It will bring almost any patient up for a time. But if I had pernicious anemia I would not be transfused, would not take the bother."

Richard Lewisohn,⁵ of New York, who has had very large experience in transfusion of blood, in commenting on the frequency with which chills follow transfusion, says that it does not seem to make much difference what technic is used, but that increasing experience with any technic tends to secure better results. He says that the most formidable chills are encountered in the treatment of leukemia and acute sepsis. "In both of these conditions," he adds, "transfusion is useless as a therapeutic measure, and sometimes causes grave danger to the patient. For this reason transfusion is strictly contraindicated in these conditions."

Copher,⁶ of St. Louis, reports a study of 245 cases of blood transfusion. He has found that by no method of blood transfusion is

it possible to avoid the varying percentage of disagreeable reactions, these reactions being manifested by fever, malaise, nausea, vomiting, chilly sensations, actual chills, muscular pains, dyspnea, cyanosis, pruritus, urticaria and headache. The fever he has found varying from 2° to 10° . He refers to a number of cases of fatal hemolysis in which the usual tests for transfusion had been entirely negative. In his own work he had 2 cases of fatal hemolysis. In 1 of these cases the blood matching before and after transfusion was perfect, but typical symptoms developed with death on the eleventh day. In the other case there had been no blood testing, but although only a small amount of blood had been transfused death occurred with typical symptoms in fourteen hours. He reports 14 transfusions for acute hemorrhage, with 11 recoveries. In 11 transfusions for hemorrhage associated with supposed shock there were 4 recoveries. Three others recovered from the hemorrhage but died later. In 12 transfusions for shock there were 8 recoveries. He warns against transfusion in pernicious anemia, where the patient is in a particularly weakened condition, because the post-transfusion reactions have been fatal in certain cases. He admits that such transfusion is without curative or permanent value. In regard to transfusion in sepsis he reports very unfavorably, quoting from several other writers. In chronic infections with secondary anemia he reports benefit in several cases, but it is apparently because of the anemia rather than the sepsis.

In a paper on fatal anaphylaxis following blood transfusions, Carrington and Lee,⁷ of Philadelphia, report a considerable number of deaths in their own practice and that of others, the deaths following usually in a few hours after transfusion, and in a number of cases at least the previous study of bloods had shown that they were entirely satisfactory. Different methods of transfusion had been used, but there seemed to have been little difference in the fatal results. Their own fatality occurred in a patient, aged seventy-five years, with pernicious anemia.

Lee,⁸ in commenting on the fatality reported by Lee and Carrington, says that following that accident he discussed the matter with a number of surgeons and found 6 other cases with similar fatal results which had never been reported. "If," he says, "in their limited experience in such a short time they have been able to unearth so many cases, it is quite evident there are many more which should be reported in order that a true estimate of the danger of this procedure can be obtained, which has now become so common that it is referred to the nurses and interns in the hospitals." Several unreported deaths have occurred in Columbus.

Recio and Ficureas (cited by Lee) report 2 deaths out of 34 transfusions, both patients dying within three hours.

Landis⁸ distinctly condemns transfusion in pernicious anemia.

He refers to Lichty's discussion on the same subject in the *Therapeutic Gazette* (July, 1923). Lichty thinks that such patients with transfusion will die sooner than those without. Each patient seems to have due him a certain number of remissions, and transfusion simply hurries him through the number to which he is entitled. He, therefore, would live longer without transfusions than with them, but in grave cases, with immediate danger, transfusion may cause the patient to rally and get over that immediate danger. He prefers, however, the old line treatment of hydrochloric acid and pepsin, with arsenic and hygienic measures.

Walter V. Brehm,⁹ of Los Angeles, states that out of 2000 transfusions, the number of patients not being given, syphilis was transmitted to 2 patients suffering from pernicious anemia, the donors in these cases having a negative Wassermann test only four or five weeks previously. He refers to a third case, also of pernicious anemia, in which the son of the patient was the donor and transmitted a violent attack of syphilis, the chancre in his case being only five days old.

W. E. Lee,¹⁰ at a joint meeting of the New York Surgical Society and the Philadelphia Academy of Medicine, said he had recently had a patient who, after very careful matching with a number of donors, was transfused by the citrate method with 500 cc of blood without any immediate reaction. One-half hour afterward, however, he developed a typical anaphylactic protein reaction with high fever, spasm of the unstriated muscles, asthmatic symptoms in the lungs with involuntary voiding of urine and several bowel movements. This subsided after one hour, but the man developed acute edema of the lungs and died eight hours after the transfusion.

Hermann¹¹ reports a case in which he transfused 200 cc of citrated blood in a patient with anemia after septic abortion. The transfusion was immediately followed by severe subjective and objective disturbances, and development of a hemorrhagic diathesis from which the patient died.

Bancroft¹³ reports a case of anuria following transfusion in which life was finally saved by decapsulating the kidneys. In his paper he refers to 8 other cases of a similar character but with a fatal result in 6.

In cases of low hemoglobin content of the blood the important question sometimes arises as to the advisability of preoperative transfusion, but no satisfactory answer can be made unless the surgeon has some idea as to the real operative risk in such cases. A most exhaustive study of this subject appeared in a paper presented to the American Gynecological Society in 1913 by Cullen, of Baltimore.¹² His report embraces all the cases in the gynecological records of the Johns Hopkins Hospital, for the previous twenty-three years, in which the hemoglobin was 40 per cent or below. He

found 170 such cases, as follows: Bleeding uterine fibroids, 42 cases; hyperplasia of the endometrium, 23 cases; carcinoma of the cervix, 18 cases; while pelvic inflammations, retained placenta, tubal pregnancy and other conditions accounted for the rest. Several of the patients were moribund when brought in, dying within a few hours without operation. The hemoglobin percentages ran from 40 to 10. There were 49 cases with hemoglobin between 40 and 36 per cent; 30 between 35 and 31; 29 between 30 and 26; 30 between 25 and 20; 14 below 20. Minor operations, such as curettage under ether or the removal of a submucous myoma, seemed to be attended with little or no trouble; 17 patients were subjected to hysterectomy, with hemoglobin as low as 19 per cent in one instance. The results, he says, "clearly show that with a very low hemoglobin hysterectomy may be safely undertaken." Of all the patients operated upon only 13 succumbed. Study of these fatalities shows very conclusively that in none of them could death be attributed to the low hemoglobin, but to certain preceding conditions or complications of which the anemia was at the most only a small part. In his conclusion Cullen says it is clearly evident that as a rule patients with a relatively low hemoglobin stand pelvic or abdominal operations fairly well. He speaks of the importance of familiarity with the technic of transfusion, but it was evidently considered unnecessary in any of the cases which he reports.

In my own work I have never hesitated for a moment in regard to operation unless the hemoglobin was extremely low. Particularly have I been free from worry since the appearance of the article by Cullen. Three cases stand out very distinctly in my experience. In one of them the patient, a middle-aged woman, had been bleeding from the bowel for several years, was emaciated, anemic and very feeble. She had been operated upon in one of our local hospitals two or three times, but on each occasion after getting the abdomen open the operator had thrown up his hands and closed the incision. She was kept in Grant Hospital for five weeks, being kept absolutely in bed, and every effort made to improve her blood. We would get her hemoglobin up to 22 per cent, and then there would be a sudden hemorrhage and it would drop down again. After doing this several times I finally decided to operate when it again reached 22. At the operation I removed a snarl of small bowel, making the usual anastomosis. Examination of this snarl showed that there had been intestinal obstruction, but Nature had overcome it by ulceration between adherent loops of bowel above and below the obstruction. The ulcer persisted, however, and it was its persistent bleeding that caused her anemia. She made an excellent recovery, and got fat and hearty. In the second case the patient's hemoglobin was 19 per cent, according to Dr. Coons' report, but he afterward told me he had shaded it a little in the patient's favor, as it was really lower than that. She was

having persistent bleeding from a large uterine fibroid. Her general condition, however, seemed to be good, heart's action good and I made a rapid panhysterectomy from which she made an uninterrupted and rapid recovery. In the third case, very similar to the second, I had thought of using radium or roentgen ray to control the bleeding, but after she was brought to the city, where I saw her for the first time, I was told by two radiation specialists that it would take probably two weeks for the radiation to be of much benefit. It seemed to me that with the persistent loss of blood it would be better to operate than to delay. Her hemoglobin was 12 per cent the day she came in; the next morning she had a pretty sharp hemorrhage, and no one knows what it was at the hour of the operation. Her husband's blood was typed and found suitable for transfusion, and he was kept just outside ready for transfusion if necessary. A panhysterectomy was rapidly made; she went through it as though her hemoglobin had been normal, made a rapid recovery and has been well every since.

Some months ago I sent a questionnaire to nearly two score of the leading surgeons of the country, and received replies from over two-thirds. Two or three of the surgeons addressed, after acknowledging receipt of the communication, had replies furnished by young assistants who were doing the transfusion. In those cases the replies, while refreshing for their enthusiasm, were in marked contrast to the replies which were furnished personally by the surgeons. The questionnaire asked as to transfusion in acute sepsis, chronic sepsis, burns, different degrees of secondary anemia, primary anemia and other conditions.

Among those who pronounced it of no value in acute sepsis were Davis (of Birmingham), Horseley, McClure, Erdman, Cabot, Seelig, MacLaren, Deaver, Bevan, Gillette, Ill, Coffey, DaCosta and Finney. DaCosta, Finney and Cabot not only regarded it as useless but even dangerous; Ochsner and Mayo as of doubtful value.

In chronic sepsis it was looked upon as valueless, or practically so, by Finney, Ill, Ochsner, Seelig, MacLaren, Deaver and Bevan. Where sepsis is attended with pronounced anemia, several of the surgeons thought it might be of some value, namely, Davis, Horseley, McClure, Erdmann, Cabot, DaCosta and Mayo.

Practically none of the surgeons used it in burns. Finney pronounced it dangerous. Erdmann and Deaver would use it only when there is anemia. Ochsner, Seelig, Bevan and most of the others had never used it.

Nearly all of the surgeons agree that transfusion is unnecessary in any of the milder forms of secondary anemia. It can be used advantageously in the more serious forms provided the cause is not some hopeless disease and the transfusion is made in anticipation of an operation. It is looked upon as especially valuable in cases of acute anemia, the result of hemorrhage. Seelig calls

attention to the danger of a serious reaction in pronounced types of anemia when the patient is on the verge and reaction may prove fatal.

In pernicious anemia practically all of them agree that it is of no permanent value, though Ochsner and Percy claim to have had some excellent results in cases in which, in addition to the transfusion, splenectomy was performed. Several suggest the possibility of error in diagnosis in cases of apparent cure.

A few of the surgeons recommend it in certain conditions of shock, though Seelig states that he is "not keen about it."

Nearly all the writers prefer the direct whole blood transfusion, though at the Mayo Clinic they use the citrate, and Frazier, of Philadelphia, is strongly in favor of it.

A few items from the correspondence might be of interest: Thus Hoover, of Cleveland, warns against the danger of more than one transfusion in cases of septicemia, and thinks the first should be undertaken with great caution. He mentions three fatalities due to transfusion in cases of sepsis. He would not employ transfusion at all except in cases where the sepsis was connected with pronounced anemia, and thinks that the improvement, whatever it is, is due to improvement in the anemia and not to increased resistance of the patient.

From the Mayo Clinic the statement is made: "Wholesale transfusion should be condemned. The circumstances connected with every case should be the determining factors in the decision."

Pfaff, of Indianapolis, reports that he has had a few cases which went wrong seemingly from embolism. One patient developed a fatal pneumonia. Three have died rather suddenly following transfusion.

Coffey commenced transfusion in 1908, and thought for some time that he was saving a lot of lives, but later experience taught him that most of these cases get well without transfusion, and he now transfuses only in cases of very low hemoglobin, and he adds that even in such cases the value is probably overestimated. He now uses transfusion a few times a year. His final paragraph reads: "It is a therapeutic measure which is probably being overworked to such an extent that the question might be raised as to whether, taken as a whole, the good it accomplishes greatly outweighs the bad."

Howard Kelly feels that transfusions are being overdone. "The temptation must be great, indeed, in many cases where the patient is ill and the doctor is anxious to do something dramatic to impress the family, and especially as the technic is comparatively simple."

Robert Abbe thinks the novelty and improved technic have excited many young men to rush into the field, and he fears that enthusiasm has run away with judgment in many cases.

MacLaren, in writing of pernicious anemia, says that some

years ago he was very enthusiastic about transfusion, but after following a large number of these cases in which transfusion was performed there seemed to be no doubt that it did these patients more harm than good, and many of the cases died earlier than they would have without transfusion.

Harvey Cushing says that his rule is to refrain from transfusion unless it is urgently called for as a life-saving measure for acute loss of blood. He adds that transfusion is used far more often than necessary and many recoveries are ascribed to transfusion which would have taken place, in some instances perhaps more rapidly, without it.

Bevan is quite pronounced in his views. He writes: "When I have seen a clinic in which dozens or scores of blood transfusions were made I felt that they were, with the exception of a very small percentage of cases, of no value, and employed without any sound indication." He cannot see any indication for it in acute or chronic sepsis, or in burns, but believes it has a definite indication in severe hemorrhage in which the hemoglobin has gone down sharply to less than 35 per cent; but even in these cases, he adds, it does not of course compare in any way with the surgical control of the bleeding if this is a possibility. His final paragraph reads: "In conclusion I would say this: Show me a clinic in which a large number of transfusions are being done, and I will show you a clinic in which a large number of unnecessary transfusions are made."

R. G. Hoskins, professor of physiology in the Ohio State University Medical Department, when asked if he knew of anything in the transfusion of blood which could physiologically antagonize infection, promptly replied that he did not. There can be no doubt that any benefit which may arise from transfusion in septic cases is due purely to the improvement in the anemia.

Conclusions. As a result of a study of the replies to the questionnaire and of the articles which have appeared during the last few years, the following conclusions have been reached:

1. Transfusion is a procedure by no means free of dangers, some of which are absolutely unavoidable.

2. It is of no value in acute sepsis, but its use in that condition is particularly dangerous.

3. In chronic sepsis its value is only in improving the anemia when that has reached a more or less dangerous point.

4. It is of no use in burns except in chronic stages when the main condition is that of anemia.

5. It is of no ultimate value in pernicious anemia, but its use is attended with more or less hazard, so that it is questionable if the end results are of any real benefit.

6. Its chief value is in conditions of profound shock or acute anemia from hemorrhage, as in postpartum hemorrhage, ruptured

ectopic pregnancy and so forth. Particularly is it of value when given immediately preceding or following some operative procedure in which acute hemorrhage forms an important factor.

7. It seems to have little or no value in shock unless that shock is the result of acute hemorrhage.

8. Its very great value in hemorrhages seen occasionally in newborn infants has apparently been conclusively established. It seems to be in such conditions unnecessary to type the mother's blood, which can be taken at once and the injection of a small amount into the vein of the infant, or preferably perhaps into the superior longitudinal sinus, may prove a life-saving procedure.

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REVIEWS.

INFECTIONS OF THE HAND. By ALLEN B. KANAVEL, M.D. Fifth edition. Pp. 499; 196 illustrations. Philadelphia: Lea & Febiger, 1925.

THE mere fact that this book has now entered the fifth edition is evidence enough of its true worth. It is, to the mind of the reviewer, the best book on the subject available to the profession. It is a well-recognized fact that infections of the hand are the worst treated surgical conditions with which we have to deal. This deplorable state of affairs is probably due to the fact that the medical profession at large does not understand the anatomy of the hand. The author has done extensive work in this most important branch of the subject, and if the reader avails himself of the information contained in these valuable pages he will obtain infinitely better results in his hand infections.

The book is replete with numerous illustrations that clarify the text to the nth degree.

No one doing surgery should be without this work.

E. E.

A MANUAL OF PHYSICAL DIAGNOSIS. By AUSTIN FLINT, M.D., LL.D., late Professor of the Principles and Practice of Medicine and of Clinical Medicine in Bellevue Hospital Medical College; revised by HENRY C. THACHER, M.S., M.D., Attending Physician, Lincoln Hospital and Assistant Attending Physician, Roosevelt Hospital, New York. Ninth edition. Pp. 320; 26 illustrations. Philadelphia: Lea & Febiger, 1925. Price, \$3.00.

THIS little work needs no introduction. It has long been a classic in the field of physical examination of the heart and lungs. Useful to the student because of its clearness and simplicity, it should be particularly valuable to the physician because of the detailed information on percussion and auscultation in diagnosis. In this the ninth edition additional emphasis has been placed on inspection and palpation and the sections on cardiac arrhythmias and incipient tuberculosis have been enlarged.

R. K.

TUMORS OF THE SPINAL CORD. By CHARLES A. ELSBERG, M.D., Professor of Neurological Surgery, Columbia University. Pp. 421; 354 illustrations. New York City: Paul B. Hoeber, Inc., 1925.

For the neurologist or neurosurgeon this monograph presents particular interest. Based upon a careful study of the clinical records of 100 verified cases of spinal-cord tumor, a comprehensive idea of the development and progression of symptoms resulting from such lesions is afforded. The histories of 81 cases are given in detail with illustrations of the sensory findings and diagrams of the position of the lesion as disclosed at operation. Individual cases are discussed and important features stressed. The second half of the monograph is given over to consideration of the typical and atypical symptomatology of tumors at different cord levels with suggestions and explanations as to the reasons for the variations noted in the development of motor and sensory changes. The importance of the cerebrospinal fluid findings in diagnosis is stressed. The indications for and technic of operative treatment is outlined and well illustrated. The author has brought the subject of the diagnosis and treatment of spinal-cord tumors up to date, possibly in too great detail to appeal to one not interested in neurology or neurosurgery. But by those dealing with such cases this monograph should be welcomed, for it contains the results of close observation and the considered opinions of an experienced neurosurgeon.

F. G.

PHYSIOLOGICAL PRINCIPLES IN TREATMENT. By W. LANDON BROWN, M.A., M.D. (CANTAB), F.R.C.P., Physician to St. Bartholomew's Hospital. Fifth edition. Pp. 511. New York: William Wood & Co., 1925. Price, \$3.75.

THIS interesting book is the work of one who is both a practitioner of medicine and a teacher of physiology. Under headings, such as "irregular action of the heart," "glycosuria in diabetes," "the work of the liver," "the principles of organotherapy," he presents briefly and concisely our present knowledge of normal and deranged physiology and the application of these facts in rational treatment. The subject is presented in a very interesting and readable form, and is for the most part complete and correct in detail. American clinicians will miss any reference to the fractional method of gastric analysis and the phenoltetrachlorphthalein test of liver function. This book should be particularly valuable to the general practitioner who has not found it possible to keep abreast of the newer literature in physiology and physiological chemistry. Its usefulness and popularity are attested to by its five editions, two reprintings and translation into the Italian.

R. K.

DIET IN HEALTH AND DISEASE. By JULIUS FRIEDENWALD, M.D., Professor of Gastroenterology in the University of Maryland School of Medicine, and JOHN RUHRÄH, M.D., Professor of Diseases of Children in the University of Maryland. Sixth edition. Pp. 987. Philadelphia: W. S. Saunders Company, 1925. Price, \$8.00.

THE sixth edition of this excellent work represents a thorough revision with many additions and changes. The subject matter has been brought thoroughly up to date and certain chapters largely rewritten, notably those on diabetes, the use of insulin, vitamins and the deficiency diseases and food allergy. A number of new tables of food analyses have been included. The book is very valuable for reference, since it is encyclopedic in its information on dietetics.

R. K.

THE EMOTIONS, MORALITY AND THE BRAIN. By C. VON MONAKOW, Zurich; authorized translation by GERTRUDE BARNES and SMITH ELY JELLIFFE. Pp. 95. Washington and New York: Nervous and Mental Disease Publishing Company, 1925.

IN this monograph the author discusses the emotions and morality from purely physiologico-anatomical and physiologico-biological standpoints. He undertakes to demonstrate that the physiological basis of the emotions and morality is to be sought, "not only in the collective activities of the structures of the nervous system, or in the cortex, that is, in the so-called 'world of ideas,' but also in the internal secretions which work in and with these structures."

The book is divided into eight chapters, is very difficult reading, and presupposes a knowledge of anatomy, biology and heredity.

N. W.

PATHOLOGY AND BACTERIOLOGY OF THE EYE. By E. TREACHER COLLINS, F.R.C.S., Consulting Surgeon to the Royal London Ophthalmic Hospital, and M. STEPHEN MAYOU, F.R.C.S., Surgeon to the Central London Ophthalmic Hospital. Second edition. Pp. 731, 4 colored plates and 306 illustrations. Philadelphia: P. Blakiston's Son & Co., 1925.

THE second edition of this well-known work contains 173 additional pages, and includes recent literature on various phases of ocular pathology. Thus, work on experimental embryology and genetics, such as the production and inheritance of developmental defects through lens antigen, is discussed.

A beginning has been made to correlate the findings of the slit-lamp with the histological picture.

The arrangement of material is like that in the first edition. Although this makes for interesting reading, various phases of a subject are so scattered throughout the pages that it is less serviceable as a reference book, especially in the absence of a complete cross-reference index. F. A.

FEEDING, DIET AND THE GENERAL CARE OF CHILDREN. By ALBERT J. BELL, A.B., M.D., Assistant Professor of Pediatrics, Medical Department of the University of Cincinnati. Second edition. Pp. 290; 11 illustrations. Philadelphia: F. A. Davis Company, 1924.

A "POPULAR" book, which in two years has had one reprinting and now appears in revised edition, needs no reviewers' opinion. Suffice it to say that this compend of childrens' "do's and don't's," diets and weights, for mothers and nurses, is plainly and concisely written. To recommend its purchase to the new mother will save the pediatrician many useless and time-consuming queries. C. L.

A TREATISE ON MATERIA MEDICA AND THERAPEUTICS. By the late R. GHOSH. Tenth edition. Pp. 718. Calcutta: Hilton & Co., 1925. A TREATISE ON HYGIENE AND PUBLIC HEALTH. By B. N. GHOSH. Fifth edition. Pp. 586. Calcutta: Hilton & Co., 1924. MATERIA MEDICA. By B. N. GHOSH. Pp. 396. Calcutta: Hilton & Co., 1923.

THESE small books are deservedly popular in India and the tropics. Earlier editions of the first two have already been reviewed in these columns. The last named, on account of the differences of British and American pharmacopeias, will not be in great demand in this country. E. K.

PSEUDO-APPENDICITIS. By THIERRY DE MARTEL, Surgeon to the Hospitals of Paris, and EDOUARD ANTOINE, Physician to the Hospitals of Paris. Translated from the French by JAMES A. EVANS, A.B., M.D. Pp. 211; 41 illustrations. Philadelphia: F. A. Davis Company, 1925.

THIS book answers the trident problem of the right lower abdominal quadrant: is it "a simple functional disorder of the proximal colon, a subacute or chronic appendicitis or a painful mechanical syndrome of the right ceco-colon?" The first fifty pages are devoted to clinical and roentgenological technique, and the rest of the book

to the clinical aspects, differential diagnosis and treatment, both medical and surgical, of the six types of "painful syndromes of the right ceco-colon." The intricate and painstaking detail of the work is a warning against the formula: "Dyspepsia plus pain over McBurney's point equals appendectomy." Lucid, conservative, based on the joint experience of physician and surgeon, it probably represents the golden mean in the modern philosophy of the right lower quadrant.

C. L.

CLINICAL MEDICINE FOR NURSES. By PAUL H. RINGER, M.D., Chief of Medical Service of the Asheville Mission Hospital, Asheville, N. C. Second edition. Pp. 306; 12 illustrations. Philadelphia: F. A. Davis Company, 1924.

IN this new edition the author has rewritten a considerable amount of material, and has introduced new subject matter on auricular fibrillation and Eggleston's method of digitalization. The author makes no claim to originality in the subject matter, but he has used considerable originality in his method of presenting it, with good effect. The material is authoritative, clear and concise. One wonders, however, just why he has not included all the diseases of the circulatory system together. Chapters III to IX are concerned with the circulatory system, as well as Chapters XXXI and XXXII. However, this is a small matter in view of the other good outstanding features of the book. He has definitely stressed the nursing care and correlated it very well with the pathology and symptomatology.

S. G.

FUNDAMENTALS OF HUMAN PHYSIOLOGY. By R. G. PEARCE, formerly Director of Medical Research Laboratory, Lakeside Hospital, Cleveland, Ohio, and J. J. R. MACLEOD, Professor in the University of Toronto, Toronto, Canada. Third edition. Pp. 349; 71 illustrations. St. Louis: The C. V. Mosby Company, 1924.

THIS is a short exposition of the various facts and theories included under physiology, as well as some histology and anatomy. It is of great benefit to beginners to have an elementary treatise written by men who have an extensive knowledge of the subject, and who select in the fulness of their judgment only the outstanding features. This is what made Huxley's elementary physiology of such lasting value to more than one generation of students. That the present book is found useful is evidenced by the demand for a third edition.

W. A.

THE EFFECTS OF INANITION AND MALNUTRITION UPON GROWTH AND STRUCTURE. By C. M. JACKSON, Professor and Director of the Department of Anatomy, University of Minnesota. Pp. 616; 117 illustration. Philadelphia: P. Blakiston's Son & Co., 1925.

THIS is an authoritative work written from the standpoint of the gross and microscopic anatomist. It is a veritable storehouse of information on the subjects of inanition and malnutrition, not only in the vertebrates, but also in the invertebrates, including the protozoa, and in plants. It is a very timely volume inasmuch as it serves to fill a gap in our knowledge, by bringing together information which has been scattered through a diversified literature. The fact that the bibliography consists of 107 pages, with an average of 25 titles to a page, is an indication of the very substantial foundation on which the book is written. In addition, extensive researches have been carried out in the author's laboratory by himself and his staff. This gives a note of assurance to the author's analyses, and enhances the value of the work. In the part devoted to vertebrates there are 25 chapters. The first describes the effects on the body, as a whole, in total inanition; the second, in partial inanition. The remaining chapters describe the effects on the gross and microscopic structure of the separate organs. It will be of especial value as a book of reference, and will be consulted not only by anatomists and physiologists, but also by pathologists and physicians.

W. A.

DISEASES OF THE MALE ORGANS OF GENERATION. By KENNETH M. WALKER, F.R.C.S., M.B., B.C. Jacksonian Prizeman and Hunterian Professor, Royal College of Surgeons. First edition. Pp. 230; 78 illustrations and 1 colored plate. London: Henry Frowde, Hodder & Stoughton, Oxford Medical Publications, American Branch, 1923.

A SMALL book devoted to andrology and purposely omitting the voluminous details of the so-called venereal diseases. The chapters deal with prostatic hypertrophy and carcinoma, chronic prostatitis and vesiculitis, genital tuberculosis, injuries and diseases of testis, epididymis, spermatic cord, penis and scrotum, with short chapters on sterility and neuroses. The book is carefully written, contains the best of modern thought and teaching and is presented in a very readable style. Some parts are especially commendable and deserve wide publicity and reading, such as how to massage the prostate, the deciding factor in varicocele, the subject of genital tuberculosis and prostatic carcinoma.

A. R.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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Distinctive Characteristics of Infections Produced by *Treponema Pertenu* in the Rabbit.—A great deal of discussion has, in the past, taken place between those who maintain that yaws is a clinical entity and those observers who hold that it is an attenuated form of syphilis. This question of the unity or duality of the two diseases, write L. PEARCE and W. H. BROWN (*Jour. Exper. Med.*, 1925, 41, 673) has been intensified by the fact that the morphological characteristics of *Treponema pertenu* and *Treponema pallidum* are similar and that infection of experimental animals with *Treponema pertenu* produced lesions closely resembling those of experimental syphilis. In order to discover if there was not some dissimilarity which had been overlooked, employing two strains of organisms of undoubted yaws, they injected a series of rabbits intratesticularly, using a technique similar to that in their syphilitic animals. The injections produced changes which differed in three essential respects from those of experimental *Treponema pallidum* infection. In the first place, and most characteristically, there was brought about an early granular periorchitis recognizable by palpation approximately three weeks after inoculation. This picture of multiple tiny nodules of the tunic without diffuse thickening of this structure has never been observed by the authors in experimental syphilis of the rabbit. Second, they find that there is no generalized manifestation of the disease elsewhere in the body, and last, a clinical lymphadenitis does not occur regularly. They note also that regression and healing of this granular periorchitis takes place in the majority of animals within three months after the original inoculation.

Jaundice as an Expression of the Physiological Wastage of Corpuscles.—It is frequently observed clinically that in the persistent obstructive jaundice of carcinoma of the head of the pancreas, the degree of the jaundice is most marked at the onset of the condition and gradually becomes less intense as the patient develops the cachexia of carcinoma. Likewise those who have worked with the van den Bergh test or the icterus index have learned to appreciate that marked bilirubinemia may be present with but slight if any icteric tint to the tissues. An explanation of these phenomena is present in a recent publication of PEYTON ROUS and D. R. DRURY (*Jour. Exper. Med.*, 1925, 41, 601). They intubated the common duct of animals and made simultaneous daily quantitative estimations of the hemoglobin and the bilirubin content of the blood before and after induced hemorrhage. It was found that a very direct relationship exists between the two and that there are definite concurrent variations in hemoglobin percentage and bilirubinemia. The jaundice that develops after experimental obstruction of the common duct expresses the physiological wastage of corpuscles from day to day. After hemorrhage there is much less wastage; consequently there is less icterus. In anemic animals there is less hemoglobin and less jaundice. As the hemoglobin regeneration takes place, the degree of icterus increases to a concurrent degree. This close relationship between the intercurrent changes in bilirubinemia and hemoglobin shows that there is a distinct barrier to the distribution of bile pigment for the blood and this lies in the bloodvessel walls themselves. The authors state that, "tissue icterus should be thought of as, ordinarily, the highly imperfect secondary expression of a condition which tends to be localized to the blood pool."

Notes on the "Thick-film" Method of Examination for Malarial Parasites.—As a result of this study in one year of over 10,000 blood films for the presence or absence of malaria parasites, T. A. SINTON (*Indian Jour. Med. Res.*, 1925, 12, 537) is convinced of the necessity of workers in this field acquainting themselves with the thick-film method of examination. He writes that while it has certain definite objections, these are more than overbalanced by the ease and rapidity with which the parasites are found by those familiar with the technique. In substantiation of his remarks as to the value of the method he quotes a large series of experiments which in round figures show that in hunting for *Plasmodium vivax* the thick film is six times as rapid as the thin film method and with *Plasmodium falciparum* approximately twenty times quicker than the older method.

The Relation of Sprue and Pernicious Anemia to Each Other and to the Monilia Psilosis.—At first blush one would without hesitance say that sprue and pernicious anemia were diseases which present totally unlike clinical pictures and would rather scoff at the suggestion that the two diseases are one and the same, differing only slightly in their manifestations. Such apparently was the reaction of some keen clinicians, judging from the discussion at the end of a recent paper by E. J. WOOD (*South. Med. Jour.*, 1925, 18, 153). However, the author presents his arguments clearly and concisely and backs them up by some experimental work which is not detailed in this article but evi-

dently reserved for a more complete report. He calls attention to the salient features of sprue, the characteristic tongue, the diarrhea, the frequent achylia gastrica, the anemia and the occasional occurrence of cord changes, symptoms all that are found in pernicious anemia. Both diseases have a tendency to run a course which is essentially chronic and which is subject to exacerbations more or less prolonged. Having presented the clinical similarity of the two conditions, the author then proceeds to discuss the etiology of the two conditions. He believes that Ashford's contention that sprue is caused by *Monilia psilosis* is well substantiated and assuming this to be true, he finds as further evidence of the unity of the two presumably different diseases, that *Monilia psilosis* is generally found in the mouth of the individual suffering from pernicious anemia. Further substantiation of this thesis is found in the experimental hemolytic type of anemia produced in animals by the injection of filtered extracts of the monilia. The chief objections to this theory of Wood as revealed in the discussion were largely objections of fact. The discussors of his paper stated that in their cases of sprue they rarely found achylia, that yeasts are not found in pernicious anemia, that the blood picture of sprue is usually of the secondary type, and that sprue is essentially a tropical disease whereas pernicious anemia has a widespread worldwide geographic distribution. The crux of the matter would seem to be in the question of the monilia causing sprue, which opinion is forcibly upheld by Ashford, or even more remotely causing pernicious anemia. Castellani holds that in sprue the monilia is merely a secondary invader and just as bacteria other than the tubercle bacilli are responsible for many of the symptoms in tuberculosis, so in sprue many of the clinical symptoms are produced by the secondarily invading yeast which is not, however, the primary cause of the disease. No matter what may be the ultimate outcome of this theory, its pronouncement by the author will undoubtedly lead to much study and eventually the etiology of the two disorders will be discovered.

Subacute Combined Degeneration of the Spinal Cord.—A. F. HURST (*Lancet*, 1925, 208, 397), at a recent meeting of the Neurological Section of the Royal Society of Medicine, discussed the relationship of pernicious anemia and posterolateral sclerosis of the cord, as observed by him in 21 cases of the latter disease. He demonstrated that the anemia which was present in this disease fulfilled all criteria for pernicious anemia, the characteristic blood picture, the glossitis, the achlorhydria all being present. It therefore seemed to the author that the two diseases are of identical pathogenesis, the disease manifesting itself in several ways according to the system involved, hemopoietic or spinal. He attributed both manifestations to the action of two different toxins, a hemolytic and a neurotoxic, which developed as a result of achylia. He argued that achylia is known to precede the development of pernicious anemia and posterolateral sclerosis. As a result of this achylia, hemolytic streptococci are admitted to the duodenum, to grow and to produce specific toxins. To substantiate this contention he showed that in a series of 42 cases of combined sclerosis and pernicious anemia from 77 per cent streptococci were isolated by duodenal drainage, whereas in 150 cases of other diseases

these organisms were found in only 21 per cent. The streptococci, moreover, were of the hemolytic type in 17 of the 19 cases of pernicious anemia and combined sclerosis in which they were examined and in the other 2 cases of combined sclerosis there was but slight anemia. That these streptococci gain entrance through the mouth is not an essential conception, but glossitis was present in 85 per cent of cases. In the discussion of this paper other observers are quoted as saying that in their series of cases achylia was not present in a goodly number of the patients. It would seem from this last statement that other types of anemia were confused with true Addisonian anemia by these observers because in this country at least hematologists are quite generally agreed this achylia is a *sine qua non* for the diagnosis of the blood disorder known as pernicious anemia.

Gastric Motor Activity in Patients with Peptic Ulcer.—M. ORTMAYER (*Arch. Int. Med.*, 1925, 35, 423) in her study of the motor activity of 29 patients with gastric ulcer lays stress upon one point about which there has always been more or less contention and which has never been satisfactorily answered, namely, the genesis of pain in gastric ulcer. She shows that the quite generally accepted theory of Carlson, that pain is the result of peristaltic contractions when the ulcer is in an "irritable state" does not hold good insofar as this can be proven by the method of recording peristaltic movement by means of an intra-gastric balloon. In 19 of the cases studied after the pain was relieved there was an increase in peristaltic movement following alkali in 10 of them, while 9 showed no change in peristaltic activity. These results would tend to show that pain and peristalsis are probably coincidental.

Experimental Morphin Poisoning.—L. C. SCOTT, F. A. LORIA and J. C. TARDO (*Arch. Int. Med.*, 1925, 35, 472) write that as there is but little known as to the manner of destruction, or at least the alteration of the alkaloid morphin within the body, they consider it worth while to investigate this problem as well as to determine if any disturbance in heart function resulted from the withdrawal of the drug in habituated dogs and, if so, to see if serum from these dogs when injected into normal dogs would produce similar changes as a result of some unknown substance circulating in the blood. The authors' first proposition, the destruction of the drug in the body, was shown by their experiments to be the result of some detoxifying action of the liver; the last premise was not proven. Incidental observations upon the action of morphin in long-continued dosage were of interest and may be briefly summarized: Immunity developed by increased dosage disappears very rapidly; whole blood does not protect an animal; morphin, as contrasted with quinin, is not abstracted from serum by the erythrocytes; morphin when injected into the portal circulation passes rapidly into the systemic circulation in some altered form.

SURGERY

UNDER THE CHARGE OF

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Splenic Anemia.—HANSAHAN (*Arch. Surg.*, 1925, 10, 639) states that it has been pointed out that there are four features of the examination that yield very suggestive information regarding a case of splenic anemia, namely, the duration of the symptoms, the blood examinations, the red blood-cell resistance and the urobilin excretion. The three most prominent phenomena following splenectomy in normal dogs, as observed by Pearce and his co-workers, were a secondary anemia, an increased resistance of the red blood cells to various physical, chemical and biologic agents and a lessened tendency to hemoglobinuria and jaundice, after the administration of hemolytic agents. The poor results following splenectomy in the acute and severe anemias, particularly in those that are pernicious in type, is probably explained by the fact that the operation does not remove the cause of the disease process. Cases with a white blood count of 5000 were considered as dividing-line cases between moderate and marked leukopenia. Cases with a marked leukopenia have a bad prognosis without splenectomy, and that this is modified by the operation is seen from the fact that 50 per cent of such patients are living. Cases having a moderate leukopenia have a good prognosis without splenectomy, while the prognosis with operation is no better than that observed in the cases with a marked leukopenia. The effect of the removal of a diseased spleen on the blood in anemia is dissimilar to the effect of removal of a healthy spleen on normal blood, as seen in experimental animals. There is an immediate and great increase in the white cell count, which gradually returns to normal in a month.

Surgical Significance of Hepatic Function.—WALTERS (*Minnesota Med.* 1925, 8, 146) says that Counsellor, of the Mayo Foundation, studying sections of liver from jaundiced animals and specimens of liver removed at operation from patients with obstructive jaundice, believes that there may be a definite ratio between the number of abnormal hepatic cells and the amount of retention of the tetrachlorophthalein in the blood stream. It seems reasonable that tests of the glycogenic or sugar-storing function of the liver might serve also as an index of hepatic function. Strauss, in 1901, gave levulose by mouth to patients with hepatic disease, and found that levulose appeared in the urine of 90 per cent, because the diseased liver could not store or utilize the entire amount. The exact role of the liver in the metabolism of proteins is not well understood. Mann has shown that on removal

of the liver there is a decrease in the amount of urea in the blood. Unfortunately there is as yet no method of measuring accurately the amount of bile salts in the blood. The 3.5 per cent of patients with obstructive jaundice, who die after operation die in most instances from a terminal renal insufficiency, due to failure to relieve the common duct obstruction adequately at operation. A few of this group, however, do not die from terminal renal insufficiency, but from a syndrome, which Parham described as hepatic insufficiency. The Rowntree-Rosenthal test of hepatic function (tetrachlorophthalein test) and the van der Bergh test of the amount of bile pigments in the blood will afford valuable aid in formulating surgical judgment and in managing patients with obstructive jaundice.

A Method of Treatment of Fracture of a Single Condyle of the Femur with Displacement Backward of the Distal Fragment to the Popliteal Space.—SUTCLIFFE (*Brit. Jour. Surg.*, 1925, 12, 450) believes that an intracapsular fracture of a condyle of the femur can be plated. The method of approach to the joint was justified by the traumatism caused by the accident (incision longitudinal on the medial aspect of the patella). The risk of an open operation was justified by the age of the patient and the importance to him of a sound knee, because of his occupation as a miner.

Some Aspects of the Endemic Goiter Problem.—OLESEN (*Mil. Surg.*, 1925, 56, 466) says that the effects of goiter are neither definitely known or understood. Consequently it is difficult to convince some persons that interference is required. Properly directed study will certainly throw much light upon this important phase of the endemic goiter problem. The treatment of goiter with iodine is neither invariably successful nor easy. In many instances of uncomplicated endemic goiter, the results are decided and gratifying. It is important that physicians acquaint themselves with the most approved methods of treating the condition and acquiring a wholesome respect for the potency of iodine. Kimball's caution that iodine be prescribed in milligrams, rather than grams, and that the toxicity of the element be considered akin to that of arsenic, is a timely admonition. It should be recalled that iodine in the form of Lugol's solution is now being extensively used, in accordance with Plummer's suggestion, in combating the crises of exophthalmic goiter and in preparing these patients for operative procedure.

Syphilis of the Stomach.—HARTWELL (*Ann. Surg.*, 1925, 81, 767) states that Chiari, in 1891, emphasized the rarity of syphilis of the stomach as demonstrated by histologic evidence. He could find only seven reported cases that he was willing to accept as beyond question. Syphilis produces actual changes in the stomach. They may be direct or indirect. The first are gummatous or simply inflammatory infiltration. Gumma may occur in both hereditary and acquired syphilis. The infiltration was seen only in the former. The indirect results due to syphilitic changes in other organs, for example in the liver or in producing the hemorrhagic diathesis, so called hemorrhagic syphilis, are relatively frequent. Gumma always apparently first starts in the submucosa

and extends from there into the other coats. Through the breaking down of the gumma, particularly because of the action of the gastric juice, ulcer and ultimately scars may form. Then only by the finding of other gummata or the remains of gummatous tissue can the syphilitic nature be established.

Tuberculoma of the Cecum.—HERRICK (*Ann. Surg.*, 1925, 81, 801) declares that there occasionally occurs in tuberculous patients a tuberculous process localized chiefly in the cecum or colon and characterized by a predominance of scar tissue and round-cell infiltration to a degree, closely simulating new growth. This process has been called hyperplastic tuberculosis, but recently authors agree on the term of tuberculoma as more descriptive. It is apparently noted more commonly in the pathologic than the surgical department. By causing chronic incomplete ileus this condition may produce a major handicap in the recovery from pulmonary tuberculosis. The chief errors both in pre-operative and operative diagnosis are, calling it appendicitis in young adults or cancer in middle or later life. Incomplete or complete ileus may furnish the first definite symptoms. In several classical cases and some reported more recently, histologic differentiation was difficult or impossible. In young adults, simple exploratory operation or an exclusion anastomosis has been followed by excellent results. Resection is preferable in good surgical risks. In an old patient where differentiation from cancer can be made, an exclusion anastomosis is preferable.

The Cancer Problem.—GROOVER (*South. Med. Jour.*, 1925, 18, 245) says that the wide discrepancies indicate that no one knows the real truth as to the surgical curability of cancer of the breast and this is also probably true with respect to all cancers. The knife has been the most commonly used instrument for that purpose and with the elaboration of surgical technic more and more tissue has been removed with the hope of attaining that objective. The limit in this direction has probably been reached and little is to be expected from a further elaboration of surgical procedure. A conservative plan of treatment gives promise of reducing practically to a minimum the present operative mortality, of saving patients an appalling number of unnecessary operations and of saving considerable added suffering following many of these operations. In radium- and roentgen-ray therapy, it is probable that the destructive action contributes in a considerable degree to the success obtained in the treatment of superficial cancers, particularly those of the basal-cell variety and this action is also operative in the radium treatment of cancer of the uterus and other tumors where it is possible to bring this substance into intimate contact with the growth by implantation or otherwise. With the advent and use of high voltage roentgen rays, there is a growing feeling among radiologists that the idea of being able to deliver a lethal dose to malignant processes, regardless of type and location is wholly misconceived. The goal of radium therapy should be not only to destroy cancer cells and restrain their activity, but to conserve and if possible activate the natural resistance to cancer invasion. The author has felt that a combination of two unrelated methods of treatment for any disease did not, as a rule, stand the test of experience and farther expressed the belief that a combination of

radiotherapy and surgery in the treatment of cancer would ultimately prove no exception to this rule. It is somewhat significant that surgeons and radiologists are now fairly well agreed that in the treatment of cancer of the uterus, it is best either to irradiate or to operate and not to do both. It is not unlikely that a similar conclusion would be reached with respect to all cancers, regardless of location were they to be subjected to the same comparative studies.

PEDIATRICS

UNDER THE CHARGE OF

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A Study of Thymus Glands.—BLISS (*Arch. Pediat.*, 1925, 42, 213) studied 1400 newborn infants, and in this number found 70 cases of what he considered dangerously enlarged thymus glands. Many investigators report that an apparently so-called enlarged thymus, which can be shown by percussion and roentgen-ray plate, is very common. The function of the thymus has not been proven. Presumptive evidence classes it with the endocrines. The topography of the thymus lends evidence to the view that part of the symptomatology may be of pressure origin. In the majority of cases a dangerously enlarged thymus presents a definite symptomatology. All apparently so-called enlarged thymus glands do not have symptoms. So-called enlarged thymus glands without symptoms are not considered dangerous. The normal for thymus gland for a baby of a give size, age and weight has not been established. The cause of thymic death has not been proven. The term symptom-producing thymus is preferable to enlarged thymus. Roentgen-ray treatment is efficient and not attended with danger. Only enough of this therapy should be used to relieve symptoms. Thymectomy has been recommended by many authors, but as a therapeutic agent it has been abandoned because of the technical difficulties encountered, and the high mortality. Radium treatment has been found to be efficient but expensive and dangerous. The roentgen ray has the advantages of cheapness and freedom from danger, although there is some question in his mind as to the danger of the roentgen rays to contiguous structures. In competent hands the danger is minimized. With the proper filters the surrounding tissues can be protected. It is said that the size of the dose required to reduce the thymus is not strong enough to be detrimental to the contiguous tissues. The lung and bronchial tissues cannot be injured by the roentgen ray.

Effects of Radiations of Cod Liver Oil.—MANVILLE (*Jour. Am. Med. Assn.*, 1925, 84, 1401) thought that the reason that rats failed to develop infections when raised on diets containing the fat-soluble

vitamins was the bactericidal radiations that are now known to characterize such fats. In order to prove this hypothesis bacterial cultures were exposed to cod liver oil. During the exposure the cod liver oil, rendered alkaline, was oxygenated. This method has been shown to increase the ultraviolet radiations. The results of these experiments strongly indicate an inhibitory action of cod liver oil on bacterial growth. A still further action of cod liver oil and such foodstuffs is seen in the effect the active principle has on cell activity. In the absence of this stimulating influence the cell remains in a quiescent or resting state. This seems to indicate that the cell is depending on this influence for the initiation and maintenance of those processes necessary for its normal activity. Normal body functions require that there be enough of this stimulating influence present to act on all the cells in proportion to their needs. Anything less than this results in a corresponding decrease in cell activity. A slight excess may result in an increase above normal; but when a marked excess is present stimulation is replaced by inhibition, if not by actual destruction. Cell activity is manifested first by multiplication, either for growth or for maintenance, and second by normal secretory activity necessary for adequate digestive processes, resistance to infections and general well-being. It will thus be seen that the results of an experiment will depend on the time in an animal's life during which the test diet is fed. When a deficient diet is fed to an immature animal growth will be stopped, the secretions will be curtailed, the reproductive organs will remain infantile and the animal will finally die of undernutrition and the effects of decreased resistance to infections. If a similar diet is fed to an adult animal its normal functions must be carried on by the residual vitamin its body has stored. As this becomes depleted the first function to be lost is reproductive ability. Further evidences of the gradual depletion of this reserve are manifested by an increasingly evident appearance of ill-being. On the other hand, when the diet contains an excess of this active principle the most marked result is sterility. As with the roentgen ray and radium, the effect of the radiations seems to be selective, the cells undergoing the most rapid cell division being the most affected. Beside the action of cod liver oil in curing or preventing rickets, we are led to conclude from the foregoing that there are two other specific actions: A stimulation of cell activity and a distinct inhibitory effect on bacterial growths; when these active substances are in excess of the amount producing stimulation there is exerted a depressing action, the most striking manifestation of which is a lack of fertility. The separation of fat-soluble A into two separate vitamins, each with a specific action, does not seem justified when the effects can be explained as being due to different concentrations of the same principle.

Skin Test for Susceptibility to Scarlet Fever.—DICK and DICK (*Jour. Am. Med. Assn.*, 1925, 84, 1477) have not observed any bad effects from immunizing doses. No necrosis, sloughing or secondary infections have occurred; nor have they observed any harmful effect on the heart, kidneys or other organs. The reactions that occur are either local or general. There is nearly always some local reaction at the site of the injection. It consists of swelling and reddening, which

appear within a few hours and begin to subside in from eighteen to forty-eight hours. The intensity of the local reaction varies with the susceptibility of the person. There may be some desquamation over the area of skin involved. General reactions, if they occur at all, seldom follow any but the first dose. They are comparatively uncommon with the dosage mentioned. They usually consist of some general malaise. Light and transient scarlatinal rashes may follow the first dose in highly susceptible persons. Lowering the dosage does not completely eliminate the possibility of a rash. Nausea of a few hours' duration is still less frequent than the rashes. The most marked general reaction has subsided in forty-eight hours, without having any after effects. Persons who have a general reaction following the first dose do not usually have any general reactions to subsequent doses. None of the reactions are so severe as those that occur during the course of immunization to either typhoid or diphtheria. If properly graduated doses of toxin are employed general reactions may follow any doses that are disproportionately large. The passive immunity conferred by prophylactic doses of scarlet-fever antitoxin is immediate, but transient. It lasts from four to eight weeks. The after-immunity produced by injections of graduated doses of scarlet fever toxin is acquired less promptly but is more permanent. Retests after immunizing doses of scarlet-fever toxin, made at intervals of from three days to one year in a series of 1634 susceptible persons have shown that immunity develops within one or two weeks. Retests have been made at intervals of one month, two months, six months and one year in persons who had been incompletely immunized with scarlet-fever toxin, so that two weeks after the last dose their skin reactions were modified but not negative. In none did the partial immunity progress to complete immunity. Before they were assigned to the care of scarlet fever patients 206 susceptible nurses were immunized to the point of a negative skin reaction. Their exposure was the same type and duration as that encountered by the nurses who had spontaneously negative skin reactions. None of these nurses, whose skin tests had been rendered negative by active immunization, contracted scarlet fever. In another series 405 susceptible persons completely immunized with scarlet-fever toxin there were no cases of scarlet fever. The exposure of these persons was direct but less protracted than that of the nurses, and many would doubtless have escaped infection without any preventive measure. Groups of persons with positive skin reactions were immunized to the points of completely negative reactions, and retested at intervals of three months, six months, one year and one and a half years. In each case the retests were negative.

Rheumatic Infections in Childhood.—COATES (*Brit. Med. Jour.*, 1925, 1, 550) thought, while subcutaneous rheumatic nodules usually make their appearance only in grave cases associated with gross cardiac disease, nodules less obvious than those of graver infection might be discovered in subacute cases. This suggestion was established in part by the examination of children known to be suffering from rheumatic infection. He examined 100 children between the ages of two and twelve years for subcutaneous nodules, irrespective of the complaints for which they were brought to the hospital. In searching for the

nodules particular attention was paid to the spinous processes of the vertebræ and to the olecranon processes. The nodules appeared to vary in size from that of a small sago grain to that of a pinhead and were often in small clusters. Synovitic creaking was often obvious around the vertebral spines, and is most characteristic. Of the 100 children 23 gave a history suggesting rheumatic infection, and in these no other causes of a toxic state could be elicited, except *Ascaris lumbricoides* in two instances, efficient treatment of which did not alleviate the symptoms.

Acute Nephritis in Children.—ALLISON (*Practitioner*, 1925, 114, 222) investigated 12 cases of acute nephritis in children, ranging in age from four to eleven years, in an attempt to discover the etiologic factors, to study the clinical course of the disease and to ascertain the after-effects. Two-thirds of the cases at the time of the onset of the illness showed markedly enlarged tonsils and adenoids, which were in a state of chronic inflammation. From the results of their removal, he was convinced that these were the etiologic factors. Clinically half of the cases showed passive hematuria, sever constitutional disturbances and slight edema. Smoky and dark concentrated urine was associated with less severe constitutional disturbance. Oliguria was not a feature in any of the cases. The functional tests were of no prognostic or diagnostic value. The blood urea was raised in one-third of the cases, the rise being temporary, and returning to normal with subsidence of the acute symptoms. The large majority of patients were free from symptoms and had apparently recovered within a month of the onset. No cases of uremia or a fatal termination were encountered. The children were reëxamined at periods ranging from nine months to a year, and were found to be healthy and to show no trace of disease.

DERMATOLOGY AND SYPHILIS

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The Wassermann Test on the Blood Serum of Pregnant Women.
—D. L. BELDING (*Am. Jour. Syph.*, 1925, 9, 132). Fetal (cord) blood gives a lower percentage of positive reactions than the maternal blood. Approximately one-third of the cord bloods of serum-positive mothers gives a positive reaction. The reaction in the cord blood is not a cri-

terion of the future reaction in the child since both positive and negative cord reactions ultimately may show the reverse in the child. Because of its weak reaction and unreliability in prognosis and because it does not permit antipartum treatment, the cord blood is unsatisfactory for routine Wassermann tests in maternity hospitals. From 25 to 30 per cent of positive reactions which occur in the sera of pregnant women are the result of technical errors from anticomplementary sera or from nonsyphilitic-fixation substances. Repeated tests of serum from pregnant women which show many transitions from positive to negative and *vice versa* furnish circumstantial evidence of nonsyphilitic fixation. A Wassermann reaction during pregnancy which varies from positive to negative may occur in true syphilis. In nonsyphilitic pregnant women a variable positive reaction may result from the anticomplementary action of the serum and nonsyphilitic fixation. As a rule these reactions are weaker and more fleeting than the syphilitic positives but no means of differentiating between syphilitic and nonsyphilitic fixation in weakly positive cases is known.

The Treatment of Psoriasis by Intravenous Injections of Salicylate of Soda.—SMITH (*Brit. Jour. Dermat. and Syph.*, 1925, 37, 33). Intravenous injections of sodium salicylate caused the disappearance of the psoriatic eruption in 16 per cent of 57 cases, its almost complete disappearance in 18 per cent, a distinct improvement in 14 per cent. Fifty-two per cent were either unimproved or worse. A maximum dose of 3.0 gm., 20 per cent solution in distilled water, was given twice weekly. Exfoliative dermatitis ensued in 6 per cent of the cases. Several difficult cases, including one which had resisted a great variety of measures, were cleared by this means. No evidence is shown of its power to prevent relapse. It is considered advisable to combine it with local treatment, which was omitted in the above series solely to evaluate the method.

Benign Lymphogranuloma and its Nature.—JORGEN SCHAUMANN (*Brit. Jour. Dermat. and Syph.*, 1924, 36, 515) states that lupus pernio and Boeck's sarcoids are identical and that these dermatoses are manifestations of benign lymphogranuloma. Benign lymphogranuloma may be present without skin manifestations. The systemic involvement occurs in the lymphatic system as shown by the presence of typical tubercles in the tonsils, frequent enlargement of the spleen and an abundant pulmonary infiltration shown only by radiography. There is a predilection of the disease for the hematopoietic system and the bone marrow is practically always involved. These medullary lesions are much more extensive than radiography would lead one to believe. A normal radiologic condition of the bones does not eliminate the presence of the medullary lesions, nor indeed even the possibility of a complete granulomatous transformation of the osseous medulla. He states that the disease is caused by the tubercle bacillus and probably by its bovine variety, though it does not present the accepted criteria of tuberculosis. The tuberculin test in active lymphogranuloma is negative. The patients frequently later become the victims of classical tuberculosis, the tuberculin reaction becoming positive and the tubercle bacillus no longer produces lesions of the lymphogranulomatous type

but classical tuberculous lesions. There is a singular immunity against tuberculosis until this change occurs. The granulomatous process disappears under the influence of developing tuberculosis. The cutaneous manifestations of lymphogranuloma are tumors, erythrodermia and prurigo, urticaria and other slight eruptions. The tumors are of the following types: Besnier's lupus pernio, Boeck's cutaneous sarcoids of the nodular, diffuse infiltrated or disseminated miliary types. The erythrodermias consist of patches of scaly redness of considerable extent and persistence in association with the systemic findings of lymphogranuloma. The author has established a symptomatic triad for the diagnosis of lymphogranuloma, consisting of histologic examination of the tonsils for evidence of granulomatous invasion; second, radiographic examination, particularly of the fingers and toes for medullary involvement; third, a negative tuberculin reaction. Hutchinson's chilblain lupus, subcutaneous sarcoid of Dárier, granuloma annulare, lupus vulgaris and classical tuberculids do not belong in the group with lymphogranuloma as proved by absence of involvement of the hemato-poietic system and a positive tuberculin test. The author does not believe that lupus vulgaris or tuberculids can coexist with the manifestations of lymphogranuloma despite reports in the literature of this combination.

GYNECOLOGY

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Nonoperative Treatment of Ureteral Calculus.—Some years ago a diagnosis of ureteral calculus usually meant that early operation was indicated, but with a more careful study of the possibilities of spontaneous passage of many of these stones conservative surgeons began to recommend watchful waiting in many of these cases. As cystoscopic technic improved, there has been an associated increase in the number of nonoperative procedures which have been recommended to favor the passage of these calculi. According to BEER and HAHN (*Jour. Am. Med. Assn.*, 1925, 84, 1028), the open operation is definitely indicated for some stubborn stones that do not respond to cystoscopic methods, especially the impacted stones that completely block the ureter, the large stones, the stones that do not move after repeated attacks of colic and those stones associated with severe uncontrollable infection of the kidney. There are, however, good reasons for avoiding open operation, whenever there is a good chance of ridding the ureter of the stone by a simpler method. They call attention to a method which they have been using and which they believe should

be used more often by the profession, especially when the calculi are in the lower half of the ureter. The method consists simply in passing a catheter beyond the stone and allowing it to remain there for from two to five days. This procedure may result in the passage of the calculus within a few hours after withdrawal of the catheter. The mechanism is not clear. Perhaps the edema of the mucous membrane which holds the stone is allowed to subside; perhaps some traction on and dislocation of the stone are caused by withdrawal of the catheter; perhaps dilatation of the ureter is the chief factor. Whatever the mechanism, it has two great advantages over other methods in this category: (1) A single treatment frequently suffices to deliver the stone, and (2) stones are passed with very little pain. Of the 27 cases in which it was tried by the authors, the diagnosis of stone was very doubtful in 1 case. Four additional cases were not favorable for the use of this method, the stone being rather large or high up in the ureter. Of 22 cases in which this method might seem to have been indicated there were 10 proved successes, or 45 per cent. Two additional patients almost certainly passed the stone in the hospital, as evidenced by cystoscopic findings before and after, but as the stone was not recovered these are not included in the 10 successes. Two other stones were passed after discharge from the hospital. In other words, out of 22 cases probably 14 successful deliveries were obtained (60 per cent). The usefulness of the indwelling catheter is emphasized by comparing their recent results with the results obtained before the adoption of this method. In a series of 114 cases definitely diagnosed as ureteral stone, 23 stones, or 20 per cent, were passed at or following cystoscopic manipulation. In this series of 114 cases occurring before the indwelling catheter was used 76 were favorable cases, and 23 stones, or 30 per cent of these, passed following one or more cystoscopic manipulations. Thus, there is a definite gain of from 50 to 100 per cent by the use of the indwelling catheter over the other cystoscopic methods they have used. It should be remembered that this method is useful only for the smaller or medium sized stones, particularly those in the lower half of the ureter. The method is practically harmless in the hands of the trained cystoscopist. Another new nonoperative method has been devised by ILLIEVITZ (*Surg., Gyn. and Obst.*, 1925, 40, 575) based on the dilatation of the ureter with air. He has constructed a catheter with a thin rubber bulb over the end, which can be inflated by means of a syringe at the other end. In the course of his experimental work the catheter was inserted into the ureter near the stone, and after repeated inflations of the catheter and gradual withdrawal of it the stone seemed to follow it downward. At the wall of the bladder, where a stone tends to become lodged, the inflations were repeated several times, and the last time the catheter was withdrawn quickly in the partially inflated condition. The stone invariably followed the catheter into the bladder. This method has not as yet been tried on the human, but the author suggests that the ordinary dental chair or operating table with stools for the feet, with the patient in the sitting position, will make it possible for the stone to come down by gravity during dilatation.

Correlation of Uterine and Tubal Changes in Tubal Gestation.—It has long been known that the occurrence of tubal pregnancy calls forth a more or less marked decidual reaction on the part of the uterine mucosa. There is, however, no unanimity of opinion as to the correlation of these uterine changes with those noted in the pregnant tube and with the clinical symptoms presented by the patient. In order to throw some light on this subject, NOVAK and DARNER (*Am. Jour. Obst. and Gynec.*, 1925, 9, 295) have presented a paper based upon the study of 21 cases of tubal pregnancy in which, in addition to the tubal gestation sac, the uterine mucosa was available for study, thus affording an opportunity of correlating the uterine and tubal changes in this connection. In 15 cases the uterine mucosa was available because a hysterectomy had been done, in 3 because a preliminary curettage had been performed and in 3 because a more or less perfect uterine cast had been expelled by the patient. The decidual reaction occurring in the uterus with extrauterine pregnancy is found to be identical with that of normal gestation so long as the embryo is alive. With the death of the latter, however, the superficial compact portion, with at times a considerable portion of the spongy glandular layer, is cast off. Its expulsion from the woman's vagina, however, may not take place for a considerable period, perhaps many days, after its separation from the deeper layers. The mechanism of the separation is strongly suggestive of that observed in connection with the throwing off of the corresponding portions of the endometrium in the nonpregnant woman at the time of menstruation. The same statement applies to the process of regeneration. In view of the degenerative and autolytic changes involving the sequestered decidua, it is not infrequently thrown off in smaller particles rather than as a large cast of the uterine cavity. They have found no evidence that the decidua merely involutes or shrinks, without loss of tissue, as has been claimed by some observers. The overwhelming majority of cases of tubal pregnancy come under observation only after the death of the embryo, and in these cases the endometrium has retrogressed from its originally decidual character. The microscopic examination of uterine curettings in such cases is of very little diagnostic value. On the other hand, the histologic study of the uterine mucosa in those cases where the pregnancy is still developing actively shows a typical decidual reaction. When curetting in a doubtful case yields such a mucosa without villi, the information gained is very valuable, though not conclusive. Unfortunately, however, cases of this type are curetted far less frequently than those of the other group, for they are characterized clinically by amenorrhea, with the possibility of intrauterine pregnancy. Decidual reaction in the tubal wall occurs in at least a fraction of the cases. It is never in any way comparable with that seen in the uterus, beings usually patchy in its distribution. Mistakes in the diagnosis of decidual tissue in such cases are frequent, for a pseudodecidual picture is common in the connective tissue from simple hyperemia or edema. Moreover great care is necessary to avoid mistaking for decidua the trophoblastic cells which invade the tubal wall so widely. In certain cases, however, the morphology of the cells is so typically that of decidual cells, their distinctness from the gestation site is so clearly discernible, and their derivation from the connective tissue so definitely

suggested by the presence of transition stages, that the diagnosis permits of no doubt. Furthermore, the occurrence of certain cases in which the reaction is noted in the nonpregnant tube of the opposite side is even more convincing. Finally, attention has been called to the not infrequent finding of islands of "ectopic decidua" on the ovary, the posterior surface of the uterus and many other locations in the pelvis, and the suggestion is offered, without as yet any definite proof, that there may be some connection between such decidual islands and the "endometrial implants" described by Sampson. The latter, it will be recalled, have pretty much the same distribution as that of ectopic decidua.

RADIOLOGY

UNDER THE CHARGE OF

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Radiographic Findings in Hepatic Abscess, Amebic Type.—J. C. DICKINSON (*Radiology*, 1925, 4, 273) reports four cases with a diagnosis of abscess in the right lobe of the liver, amebic in type. The best method of examination is with the fluoroscope, which shows the right diaphragm to be elevated and its excursion limited or absent. The right costophrenic angle is increased in acuteness and if the abscess is near the superior surface of the liver, a rounded elevation can be seen in the diaphragm. The whole liver shadow is enlarged. If the abscess ruptures into the pleural cavity, the picture may be that of a pleural effusion. If this results in an empyema differentiation may be impossible until the pleural cavity is drained. If it has ruptured into the lung, localized consolidation followed by expectoration of amebic pus is quite characteristic. In a certain proportion of cases there is a characteristic collection of gas between the dome of the liver and the diaphragm.

Roentgenotherapy of Vascular Nevi.—Unfiltered rays of medium penetration (5 to 6 Benoist) in moderate doses (never exceeding 4H) given at three sittings with an interval of three or four weeks will give good results in vascular, tuberous nevi, according to F. BARJON (*Jour. de Radiologie et d'Elect.*, 1925, 9, 15). Only tuberous nevi should be thus treated; one should never apply radiotherapy to flat nevi. Treatment should begin early, preferably in the first six months of age. In all cases there is a disappearance of the tumor and the discoloration, and in favorable cases the esthetic result approaches perfection.

Diagnostic Pneumothorax.—Pneumothorax is a valuable aid in the diagnosis of thoracic pathology, especially pathology of the mediastinum, pleura, lungs, ribs, and the chest wall, according to HARRY J. ISAACS (*Am. Jour. Roentgenol. and Rad. Ther.*, 1925, 13, 3). Diagnostic

pneumothorax is especially indicated in lung tumors. If the injection of air into the pleural cavity causes a complete separation of the lung from the costal pleura, it speaks for a lung tumor, while extensive adhesions (failure of lung to collapse) speaks more for an interlobar empyema with pleural thickening. The same technique as for therapeutic pneumothorax is used. Complications reported in the therapeutic work are pleural shock, perforation of lung, infection, pleural effusion, air embolism, and subcutaneous edema, but are very rare. Of the 2 cases reported by Isaacs, the roentgen-ray report of the first described a large shadow occupying the left lung filled from apex to ninth rib, posteriorly, with left apex and the mediastinum obscure. After injection of 650 cc of air the radiograph showed a tumor mass well defined. The lung tumor, diagnosed as sarcoma, decreased considerably after roentgenotherapy. In the second case the roentgen-ray report described a dense shadow in the right side of chest from clavicle to sixth rib, regular in outline and irregular in density, merging with the cardiac shadow after injection of 650 cc of air the radiograph showed a compression of the lung and complete separation of the pleura from the lung tissue. Diagnosis of primary pulmonary malignancy was made.

A Congenital Anomaly of the Patella. Separation of a piece or pieces of bone from the patella as a congenital anomaly is frequently misinterpreted as fracture of the patella, according to A. W. GEORGE and R. D. LEONARD (*Am. Jour. Roentgenol. and Rad. Ther.*, 1925, 13, 3). In six cases they have found the fragment or fragments in the upper outer quadrant of the patella, being smooth in outline, and having a periphery of cortical bone. Usually the deformity is present in both patellas, therefore, the opposite patella should always be roentgenographed in case of abnormality of one. Failure to make correct diagnoses in these cases has caused insurance companies to pay compensation for many weeks, believing the patient to have a fractured patella.

Further Experience with Tetrabromphenolphthalein Sodium Salt in the Roentgenologic Diagnosis of Gall-bladder Disease.—The intravenous injection of tetrabromphenolphthalein sodium salt is of value in roentgenographic examination of the gall bladder according to W. H. STEWART (*Am. Jour. Roentgenol. and Rad. Ther.*, 1925, 13, 3), because it is a method that outlines the gall bladder, showing its size, shape, emptying power and the presence of gall stones. An ampule of 5.5 gm. of the salt is dissolved in 40 cc of freshly distilled water by heating and administered intravenously in two doses, 20 cc first and repeated in a half hour. The toxicity of the salt, few patients escaping its unpleasant reactions, is the chief objection to this method of gall-bladder diagnosis and special attention to its prevention has been given by Stewart. Contraindications are cardiac patients, diabetics, and those suffering from severe constitutional diseases. Highly emotional and neurotic patients should be avoided. Best results have been obtained by a thorough cleansing of the intestinal tract, besides a starvation diet on the day before administration, then a hypodermic injection of fifteen minutes of adrenalin (1 to 1000 solution) a half hour before the first intravenous injection. Although the reaction has been very severe in some cases there have been no deaths from this preparation. Films

are made at eight, twelve and twenty-four hours after administration of the dye. In 36 cases checked up by operation, Stewart has found that deformity and malposition of the gall bladder usually indicates disease, and that if no shadow is obtained it is due to one of the following reasons: (1) Obstruction of the cystic duct; (2) contents of gall bladder do not mix with the dye; (3) too little bile to cast a shadow; (4) too much content diluting the dye, and (5) poor liver function.

The End Results in Roentgen-ray Treatment of Cutaneous Cancer.—In a series of 144 selected patients with skin cancer 93.6 per cent cures were obtained with roentgen-ray treatment by H. H. HAZEN and E. R. WHITMORE (*Am. Jour. Roentgenol. and Rad. Ther.*, 1925, 13, 2) or 96 per cent cures of 225 selected growths. Skin cancer is more common in men and the results are better in women. Deep ulcers and nodules are not as favorable as other types; also, growths of the ear and in cartilage give poor results. The age of the patient does not affect the result materially but early lesions give better results than old, and small lesions better than large. The roentgen ray gives the same results as radium and surgery, but cases previously irradiated gave only 50 per cent cures. The authors have found a one-and-a-half-unit dose as effectual as a two-and-a-half-unit dose, giving at least three or four treatments to all cases or more if necessary. They found that 94 per cent of the recurrences appear in the first year and that the causes of failure are deep invasion of cartilage, poor coöperation, localization in scar tissue and previous radiation. Prickle-cell cancers resulted in 45 per cent cures and of cancerous glands, 41 per cent cures. There are a number of theories of the mechanism of cure of skin cancers and the view held by the authors is that the cure of cancer depends upon a proper stimulation of tissue reaction and that the mode of action of irradiation is through its effect upon the healthy tissue, not upon the cancer.

Value of Radium and Roentgen Radiation in the Treatment of Benign Uterine Hemorrhage.—Benign uterine hemorrhage, from the standpoint of treatment with radium and roentgen radiation can be divided into four classes according to HARRY E. BUNDY (*Am. Jour. Roentgenol. and Rad. Ther.*, 1925, 13, 2), namely, fibroids, essential menorrhagia, bleeding following inflammatory adnexal disease, and pernicious bleeding during gestation. Small fibroids should be treated with radium; those the size of a first trimester pregnancy respond best to roentgen radiation or a combination of radium and roentgen ray; while larger fibroids should be treated surgically if possible. The danger of producing a menopause should always be borne in mind. The author has been using in young women 300 to 600 mg. element hours, repeating if necessary. Essential menorrhagias respond very readily to the radium rays. The bleeding from adnexal disease, often quite intractable to ordinary forms of treatment, has yielded quite uniformly to roentgen radiation over the spleen. The author has also adopted this radiation for pernicious bleeding of gestation, and has had good results in all but 4 cases out of 33, using a 15 per cent dose delivered to the spleen, repeated in forty-eight hours if hemorrhage persists, giving then a two-thirds erythema skin dose.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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An Exotic Strain of Encephalitogenic Virus.—A virus obtained from the cerebrospinal fluid of a patient suffering from vascular and neural syphilis, and who never presented symptoms of epidemic encephalitis, is described by FLEXNER and AMOS (*Jour. Exper. Med.*, 1925, 41, 215). This virus is indistinguishable from the so-called virus of encephalitis on the one hand, and from the virus of febrile herpes on the other. Hitherto, these two viruses have been described as the encephalitis-inducing agents. This work lays the conclusions from all preceding studies open to question. Specimens of cerebrospinal fluid numbering 100 were used in the investigation, of which 27 were derived from patients diagnosed or suspected as being cases of epidemic encephalitis, and 73 from cases of a miscellaneous character. Of this series, from only 1 was a virus obtained (known as their "J. B." virus) which was capable of producing experimental encephalitis in rabbits, and this, as noted above, was from a case of syphilis. Inoculations were made into rabbits by the following routes: Intracranial, corneal, skin, blood, nasal and testicular. Type protocols are given in each instance. Throughout these procedures the "J. B." virus demonstrated its potency and its close relationship to the previously described encephalitis-producing viruses. In reviewing the histology of "virus encephalitis" the authors report a marked disparity in the findings, these being due in great part, they suggest, to the mode of inoculation in which several factors may coöperate; trauma, positively chemotactic tissue elements and virus. Furthermore the rabbit itself very often exhibits, even in health, a variety of encephalitis, a factor which may have misguided some investigators. In studying the cerebrospinal fluids derived from the 27 cases of suspected epidemic encephalitis they failed to produce the disease or to confirm the results obtained by other workers. They conclude that their "J. B." virus is, in reality, a herpes virus that found its way into the cerebrospinal fluid. They also make the suggestion that all viruses hitherto described are of the same nature, thus making the etiology of epidemic encephalitis entirely unresolved, and that to ascribe the disease to the herpes virus is, they believe, at the present time entirely unwarranted.

Herpetic Strains of Encephalitogenic Virus.—In this paper FLEXNER and AMOS (*Jour. Exper. Med.*, 1925, 41, 233) endeavor to demonstrate the similarity of the encephalitis virus to that of febrile herpes. A somewhat similar idea has been offered by Levaditi, Nicolau and Poincloux, who, however, merely suggest the name of "herpetic-encephalitic" virus to embrace a group of viruses of which a neuro-

tropic variety constitutes the provocative virus of epidemic encephalitis. Furthermore, in order to produce this disease in man a mass modification of the soil (nervous system) and the prevalence of this specially adapted virus are necessary. To the conjunction of these two factors is ascribed the several outbreaks of epidemic encephalitis in many parts of the world in the past few years, and this explanation of the etiology is questioned by the authors of the present paper. Several strains of the virus of febrile herpes were used in the experiment, of which one, the "H. F.," was principally studied. It was taken from a fresh herpetic vesicle on the lip of a subject very prone to attacks of febrile herpes. This strain was capable of producing typical symptoms of "virus encephalitis" in rabbits, to which they succumbed. The strain was studied for a period of three years, during which time it was compared with the "J. B." virus previously described, the Levaditi virus *souche* C., the Doerr and Basel virus and the Goodpasture strain, Micrococcus virus. Illustrative protocols are given of rabbits inoculated by the intracranial, corneal, skin, nasal, intravenous and intratesticular routes. Guinea pigs, rats and mice were also used in the study with some modifications of the findings. They find that the "H. F." strain exhibits a degree of encephalitogenic power not exceeded and rarely equalled by any strain of the so-called encephalitis virus, and "virus encephalitis" invariably follows inoculation by any of the routes described. The virus is also glycerol-resistant, is filterable through Berkefeld candles and behaves immunologically as do the usual strains of herpes and encephalitis virus. They conclude that the encephalitogenic power is not a special property of virus secured from cases of epidemic encephalitis, and that different properties, such as dermatotropic and neurotropic, may be ascribed to differences in potency.

The Pathology of the Hypophysis.—This is the first of a series of studies on the pathology of the hypophysis and deals with the presence of abnormal cells in the posterior lobe. For some years past SIMONDS and BRANDES (*Am. Jour. Path.*, 1925, 1, 209) have made serial sections of all hypophyses removed at necropsy. The groups of cells are fairly well circumscribed, nonencapsulated masses of cells varying in size from less than 0.25 mm. to 1 mm. in diameter. They are located in the posterolateral quadrants of the neurohypophysis, and are in general similar to those reported by Sternberg and by Priesel. The cells are large, round, oval or polygonal cells which stain a bluish purple and have abundant granular cytoplasm. The nuclei are round and usually placed eccentrically. Frequently they are deeply stained and pyknotic, or they may be pale and apparently undergoing karyolysis. Some of the cells are devoid of nuclei; others show shadowy nuclear remains. No nucleoli were seen within any of the cells. The stroma was scanty and similar to that of the posterior lobe. The total quantity of blood-vessels within these areas is very small. The authors are not convinced that these masses of cells are true neoplasms, but without being dogmatic they believe rather that the lesion is a localized retrogressive change in the glia cells to which they relate the large cells of this lesion because many of the cells give off from their surfaces fine branching processes which take part in the formation of the inter-

cellular fibrillar meshwork. They point out that the lesion is found more commonly in the later decades of life. Moreover some of the cells in these lesions are undergoing degeneration or even necrosis, as evidenced by the character of the cytoplasm and of the nuclei. While the cell masses are minute they occupy a relatively considerable proportion of the neurohypophysis and may consequently produce some alteration of its function. The clinical notes in the cases they reported were incomplete and failed to disclose any of the functional or bodily changes usually ascribed to lesions of the hypophysis, but they point out that a more careful study of the patients with this pathological process in mind may reveal some clinical manifestation ascribable to it.

Concerning the Microscopic Structure of the Hypophysis Cerebri in Acromegaly.—In the belief that, if acromegaly is a disease entity, the adenomatous change which takes place in the hypophysis should show constant histological characteristics, BAILEY and DAVIDOFF (*Am. Jour. Path.*, 1925, 1, 185) undertook a critical study and analysis of the material available at the Peter Bent Brigham Hospital. They recommend fixation of the hypophysis cerebri in Regaud's fluid, and for a differential stain to demonstrate the *a* and *b* granules they prefer the acid fuchsin-acid violet method of Bailey. They point out in detail the errors of interpretation that may arise from other methods of fixation and staining. The report is based upon a study of the tissues removed at operation from 35 patients with symptoms of acromegaly. Four of these cases are reported in detail with plates, including roentgenographs. As a control they also report their findings in 54 cases of adenomatous enlargement of the hypophysis with dyspituitarism but without acromegalic manifestations. In general they found that in cases of acromegaly in which the gland reaches a size sufficient to demand an operation a constant pathological change had taken place in the anterior lobe of the hypophysis. This change consisted of an adenomatous formation composed of cells containing *a* granules. The cells lay in a loose mass practically without stroma and with very little blood supply. The normal columns of cells were wanting. The cells themselves varied greatly in size and some of them contained as many as half a dozen nuclei. Many of the cells tended to flatten along the surface of adjacent cells in the form of crescents. The *a* granules were finer than normal and showed a tendency to collect in the periphery of the cytoplasm. The increase in the *a* granules was definitely present in 31 of the 35 cases studied. In the remaining 4 cases no *a* granules could be proved, but in 3 of them the cells contained coarse granules which were definitely not *b* granules, although they could not be differentiated clearly as the *a* type. In the fourth case a diagnosis of acromegaly was not made at the time of operation, but the patient returned later with characteristic changes and died in diabetic coma. No necropsy was obtainable. On the other hand in the 54 cases of adenomatous enlargement of the hypophysis without acromegalic manifestations practically no *a* granules could be found even after a long search. The cell boundaries were indistinct. The cells were arranged in thick columns separated by septa of connective tissue. The cells were elongated and of the chromophobe type, having no granules other than mitochondria. Each cell had a simple elongated

nucleus. In addition to these cases they have reviewed the literature including only those cases in which sufficient details of the histological technique were given, so that one could be sure that it was adequate for the demonstration of *a* granules. In all 23 cases were reviewed, and of these 17 definitely showed an increase in the *a* granules. Of the remaining 6 cases, 3 showed an increase of the eosinophilic cells with multinucleation, 2 showed multinucleation, while the sixth presented cells with fine granules, the cells not being arranged in alveoli. They thus believe that in acromegaly there is a definite histological change in the pars distalis of the hypophysis cerebri.

HYGIENE AND PUBLIC HEALTH

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Results Obtained with the Dick Test Before and After Immunization with the Toxin of the Hemolytic Streptococcus of Scarlet Fever.—DYER and SOCKRIDER (*Pub. Health Rept.*, 1925, 40, 593) tested groups of white and of colored boys in an institution, and found 17.1 per cent to be susceptible to scarlet fever, according to the Dick test. These were immunized by three injections of scarlet-fever toxin and about 80 per cent were rendered negative to a subsequent test with the toxin. The presence of a preservative, 0.5 per cent phenol, seemed to have no adverse influence on the immunizing properties of the toxin. A heated toxin and the medium alone, used as controls of the test, were compared, but without conclusive evidence of the superiority of either.

Tetanus from Vaccination Dressings.—The Public Health Service (*Pub. Health Rept.*, 1925, 40, 559) issues a warning against the use of bunion pads as a dressing in vaccination against smallpox. This singular use of bunion pads appears to be more common than would be supposed. Several fatal cases of tetanus following their use have recently occurred in the United States, and laboratory tests have demonstrated the presence of tetanus spores in bunion pads from the same source as those which were associated with tetanus cases. The Public Health Service deprecates the use of any kind of a shield as a vaccination dressing. The employment of such a shield tends to prevent evaporation, to retain heat, moisture, or discharges, with a consequent softening of the vesicle, to obstruct lymphatic drainage, to

produce hyperemia and to create conditions apparently favorable for the development of bacterial invasion, especially by the tetanus organism. The smallest single site insertion compatible with a successful take and with no immediate dressing whatever is believed to be the best method of vaccination in the majority of cases.

Absence of Transferable Immunizing Substances in the Blood of Morphin and Heroin Addicts.—DUMÉZ and KOLB (*Pub. Health Rept.*, 1925, 40, 548) review briefly the claims of those who consider that that is an immunological basis for drug addiction. In the authors' experimental work the serum of morphin and heroin addicts was used to determine whether or not it had any protective influence on the effect of doses of morphin or heroin in white mice. In every case the results were negative, that is, no protective influence was manifested by the serum of addicts when compared with that of nonaddicts.

Mild Typhus (Brill's Disease) in the Lower Rio Grande Valley.—SINCLAIR and MAXEY (*Pub. Health Rept.*, 1925, 40, 241) observed twenty cases of Brill's disease, all of which recovered. The Weil-Felix reaction with *B. proteus* was positive in the large majority of cases. While the source of the epidemic could not be traced, it was in some instances possible to demonstrate close association between cases. The authors failed to find body lice associated with any case, and state that lice do not thrive in the Rio Grande Valley, at least during the summer months. On the contrary, head lice are common though it is not stated that these were associated with any of the cases.

The Incidence of Illness in a General Population Group—According to SYDENSTRICKER (*Pub. Health Rept.*, 1925, 40, 279), a population of between 8000 and 9000 was kept under observation for two and a half years, including 1600 families made up of 87,200 white persons for the entire period. The method used was that of house-to-house canvass and the collection of data from collateral sources. The data are summarized as follows: Summary: A true picture of the ill health, and therefore, of the problems to be attacked by those who are engaged in preventing disease, is not adequately portrayed by death statistics. The obvious reason for this is that mortality records by definition do not include the cases of illness that are not fatal, to say nothing of the suffering and the lowered vigor and the lessened efficiency among the living. A study of illness in a general population group in a typical small city not only shows the inadequacy of mortality statistics for this purpose, but suggests the kind of picture that complete morbidity records would afford. Looking at it in broad outline only, it was found in the group of persons studied that: (1) Over 100 cases of illness occur annually for each death. (2) More than half of the morbidity was due to respiratory diseases; the ratio of respiratory illnesses to deaths from respiratory causes was more than 300 to 1. (3) Diseases and disorders of the digestive system caused an annual illness rate of 117 per 1000 but a mortality rate of less than 1 per 1000, a ratio of about 200 to 1. (4) The "general diseases"—epidemic and nonepidemic—composed principally of those diseases against which public health effort has been mainly directed, caused only 11 per cent of all

illnesses. (5) While deaths occur principally in infancy and in old age, ill health, as measured by the incidence of illness, occurs with comparatively little variation throughout life; it is prevalent among the young, those in the "prime of life" and the aged without much discrimination. This picture inevitably suggests a point of attack upon the causes of ill health not adequately recognized now—the diseases which are incident between the extremes of life. If, as it is now the custom, success of public-health work is to be measured in money terms, surely no more cogent argument could be put forward than that of the economy of preventing loss of the efficiency of the population at those ages when health means the most in production. It is not hard to figure that a day of sickness prevented at the age of thirty or forty years is more profitable than at the age of seventy. But, in a broader sense, the diseases which cause ill health are a challenge to the sanitarian, not merely because they have an exhausting effect upon man's power to resist death but because they lessen his ability to achieve and his capacity to enjoy life in the years of his most abundant strength.

Studies on the Industrial Dust Problem—GREENBERG (*Pub. Health Rept.*, 1925, 40, 292) shows clearly that certain dusty trades result in an excessive prevalence of tuberculosis compared with the population in general. The highest tuberculosis mortality is found in marble and stone cutters, where it reaches 540.5 per 100,000. This is compared with a rate of 236.7 for all occupied males and 111.7 for farmers and farm laborers. In the state of Vermont the incidence, as might be expected, is excessively high in the granite cutters. In Connecticut, among ax polishers and grinders, the tuberculosis mortality is over ten times that of the state in general. Lime dusts and brick dusts seem harmless, and the same is true of cement dusts and coal dusts—indeed, the latter appears to be beneficial rather than otherwise so far as tuberculosis is concerned.

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ORIGINAL ARTICLES.

A CONSIDERATION OF THE CLINICAL VALUE OF EPHEDRIN.*

WITH A REPORT ON ITS EFFECTS IN CERTAIN SPECIAL CASES.

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I. Introduction. EPHEDRIN is the name given to an active principle isolated by Nagai¹ from an Asiatic drug, Ma Huang (*Ephedra vulgaris* var. *helvetica*), which has been used in the practice of medicine in China for more than five thousand years. In chemical composition it is closely allied to epinephrin and the recent comprehensive study of its physiological effects in animals and man by Chen and Schmidt² has showed that it is possessed of sympathomimetic actions to a conspicuous degree. It differs from epinephrin, however, in that the action of a single dose may persist for several hours, and it is reliably effective when given orally or by hypodermic injection.

The discovery of the physiological activity of extracts of the medulla of the suprarenal gland, the isolation from it of a crystalline principle possessing intense and characteristic power and the conception that this substance is a hormone which takes part in the normal adjustments of the organism to unusual strain and is supplied to it in varying amounts led to the hope and to the expectation that a new agent of unique power was available to the physician in the rational treatment of various bodily disorders. This hope and expectation have only partially been realized and important reasons

* This investigation has been made with the assistance of a grant from the Committee on Therapeutic Research, Council on Pharmacy and Chemistry, American Medical Association.

are to be found in the evanescence of its action and in the uncertainty of its effects when given by other methods than that of intravenous injection.

The discovery of another substance, ephedrin, possessing a persistence of action many times greater than that of epinephrin and capable of effective utilization by either oral or hypodermic administration, may properly renew the hope of clinical effectiveness which the latter drug has not fulfilled. With this thought in mind, a supply of ephedrin having become available,* I have undertaken a study of its effects in selected patients in the University Hospital. Before describing the results a résumé of the known pharmacology of this drug may be useful.

II. **Résumé of the Pharmacology of Ephedrin** ($C_6H_5 \cdot CHOH \cdot CH(CH_3)NHCH_3$). Mydriasis by ephedrin, with little change in accommodation or intraocular tension, was first observed by Miura³: rise of blood pressure and inhibition of intestinal movement by Amatsu and Kubota.⁴ Chen and Schmidt showed that vasoconstriction and cardiac stimulation were responsible for the rise in blood pressure: they found that the uterus was stimulated and the bronchial muscle relaxed, and that during ephedrin mydriasis the pupillary light reflex was retained. The effects of a single intravenous injection persist for at least fifteen minutes and often much longer. To elicit similar effects by subcutaneous injection more than 10 times the intravenous dose is required. Effective absorption from the intestinal tract was proved.

The low toxicity of ephedrin was observed by Miura, by Chen and Schmidt and most recently by Chen.⁵ The minimal lethal dose for rabbits, cats and dogs is from 30 to 100 times that required to produce conspicuous action. Daily administrations of large doses to rabbits for four weeks resulted neither in tolerance nor in detectable injury.

In the treatment of experimental shock in dogs, Chen showed restoration of the circulation by intravenous injection of 2 to 3 mg. per kg. Similar action was observed after hemorrhage.

Chen and Schmidt demonstrated rise of blood pressure in normal man following 60 mg. given subcutaneously or by mouth, with no untoward results: they also secured evidence of favorable action from a single dose in a patient in moderate surgical shock and from repeated doses in a patient with Addison's disease.

In one phase of its action on the circulation ephedrin differs from epinephrin: after repeated doses have been given to animals, further injections may be followed by lowering in blood pressure,

* The ephedrin used in this study was made in the laboratories of the Peking Union Medical College according to the method of K. K. Chen and under his supervision and was made available to me by the department of pharmacology of this University. I am indebted to Dr. Carl F. Schmidt of that department for much helpful advice during the course of these observations.

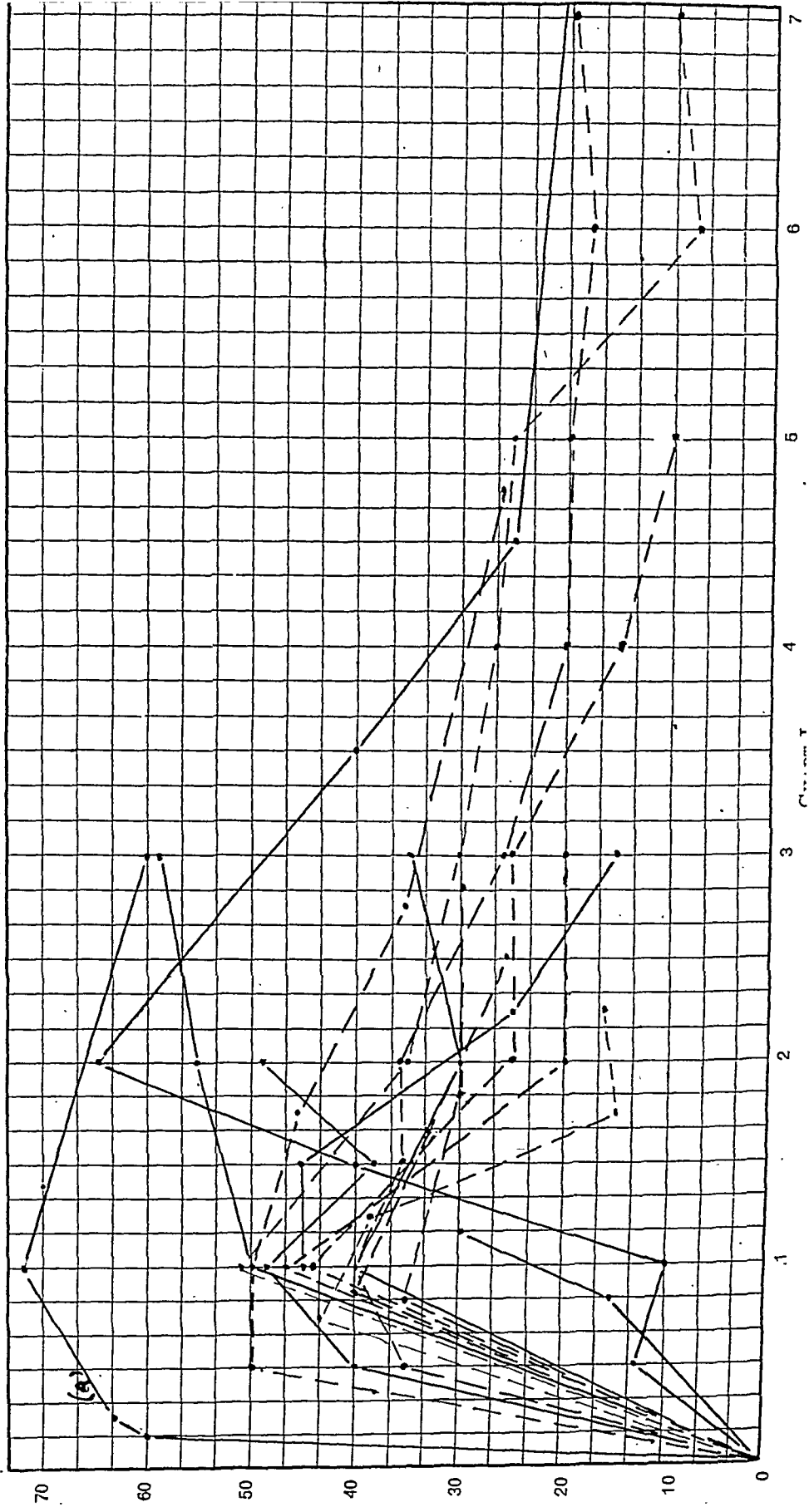
due, presumably, to depression of the heart. Intravenous injection of a large dose, therefore, in conditions of circulatory failure might be dangerous.

III. General Observations. Eighty-four acute clinical experiments have been made under controlled conditions; in other instances, the drug has been administered over long periods but without such careful supervision. Intelligent and coöperative patients were selected because a reliable account of subjective symptoms was desired in addition to the objective observations planned. Each acute experiment was made in the forenoon; the patient had breakfast before receiving the drug except in instances in which hourly urine collections were obtained; in those, breakfast was omitted. The majority of patients while under observation were kept quiet in bed; a few were seated in a chair, undisturbed as far as possible. Doses of ephedrin sulphate, ranging from 50 to 125 mg., were given orally or subcutaneously (in one case intravenously). Each patient was kept under close personal observation for a number of hours after administration of the drug.

The results obtained on this selected group of patients are summarized in Table I. The cases are arranged in descending order of the maximal increase in systolic blood pressure (ninth column). The data include sex, age, clinical diagnosis, dose of ephedrin and method of its administration, systolic blood pressure before the drug and highest reading after, the corresponding pulse rates, effects on heart as indicated by study of cardiac murmurs and certain special subjective and objective effects.

No definitely harmful effects occurred in any patient; a certain few complained, usually on being questioned, of palpitations or throbbings, of nervousness and rarely of a little nausea. Two vomited about ten hours after hypodermic injection; both were of a very nervous type and it is not certain that the ephedrin was causative. One who had evidence of marked myocardial degeneration showed a transient pulsus alternans about one hour after his injection. There were no other unfavorable phenomena and the patients did not object to taking the drug repeatedly; some felt distinctly stronger and better after receiving it. These observations agree with those of Chen and Schmidt concerning the slight toxicity of the drug.

(a) *Effects on Blood Pressure.* The most consistent results were obtained in reference to the systolic blood pressure. The observations were made at half- to one-hour intervals, and the maximal rise occurred within an hour when the dose was given subcutaneously and usually within two hours when the administration was oral. In the 84 instances, including only 2 presumably normal persons, some elevation occurred in 70; in 57 the rise amounted to 10 or more mm. of mercury, in 49 to 15 or more, in 37 to 20 or more, in 29 to 25 or more, in 21 to 30 or more and in



15 to 40 or more. In 1 instance of acute peritonitis in which no pulse or blood pressure could be detected before giving the ephedrin a systolic pressure of 65 mm. and a diastolic of 50 mm. was obtained fifteen minutes after 100 mg. of the drug had been injected into a jugular vein. In 13 cases no rise occurred and in 6 of these there was an actual fall (the greatest drop amounting to 20 mm.). The clinical condition of these patients afforded no obvious explanation of this fall, but it is probable that the original level was unnaturally high because of their nervousness in the beginning of the experiment.

The duration of the systolic blood pressure rise varied: usually after reaching its highest point within one to two hours it slowly fell during the next three or more hours to the original level. In many instances, however, some elevation above the original level persisted after six or eight hours. Chart I shows the type of curve obtained.

This chart also shows that the extent of rise after oral administration is as marked as after subcutaneous injection, though, as stated, the action is somewhat more promptly elicited by the latter method. Of 69 cases (2 to 70) which showed increase in systolic pressure, 26 received the drug by mouth and 43 subcutaneously.

The diastolic pressures are not recorded, since they were not at all consistent, but it may be stated that they usually rose with the systolic though not to a comparable degree. Often they remained approximately the same throughout the experiment.

(b) *Effects on the Pulse Rate.* The pulse rates recorded were determined just before the ephedrin was given and at the time the maximal systolic blood pressure observation was made. The latter was not in every instance the lowest rate obtained but usually it was. In most cases there was strictly an inverse relation between these two phenomena, the pulse rate decreasing as the blood pressure rose, and the two came back to the original level at about the same time. This was not invariably true, however, and in 16 cases a definite increase in the pulse rate occurred. It is obvious that the direct stimulant effect of ephedrin on the cardiac accelerator mechanism is apt to be antagonized by the cardiac inhibitory action of increased blood pressure. In anesthetized animals, in which the vagus mechanism is depressed, the former action predominates; our observations indicate that in man the compensatory vagus effects are more apt to be encountered.

CHART I.—Curves of systolic blood pressure increase obtained on patients who showed a maximal rise of 30 or more mm. of mercury after the administration of ephedrin. The base line represents the level of blood pressure before ephedrin; the ordinates, therefore, show not the actual blood pressure, but the rise above the original level in mm. of mercury. The abscissas represent time intervals, the figures indicating hours. The solid lines were obtained after oral administration and the broken ones after subcutaneous injection. Curve (a) was obtained after intravenous administration. (See Case XIII.)

TABLE I.—GENERAL SUMMARY OF DATA OBTAINED IN REFERENCE TO 84 ACUTE CLINICAL EXPERIMENTS WITH EPHEDRIN. THE FOLLOWING ABBREVIATIONS ARE USED: IV. = INTRAVENEOUSLY; SC. = SUBCUTANEOUSLY; O. = ORALLY; INC. = INCREASED; DEV. = DEVELOPED; P. = PULMONIC AREA, AND A. = AORTIC AREA.

No.	Sex.	Age.	Clinical diagnosis.	Ephedrin administered.		Systolic blood pressure in mm. Hg.				Pulse rate.		Systolic murmurs.	Special effects.
				Amount in mg.	Method.	Before.	After.	Maximal increase.	Before.	After.			
1	M.	42	Acute peritonitis	100	Iv.	?	65	65	140	132	None	Heart sounds became clearly audible. Died 12 hours later.	
2	F.	39	Neurasthenia	100	0	115	125	65	80	64	Inc. at apex, dev. at base	Nervous. Heart sounds louder.	
3	M.	22	Arthritis deformans	100	0	100	158	58	68	80	Dev. at all areas	Vital capacity increased 50 cc.	
4	M.	16	Convalescent pneumonia	100	Sc.	115	165	50	66	66	Dev. at P. and apex	Nervous.	
5	M.	18	Gonorrheal arthritis	100	Sc.	95	145	50	52	52	Blood sugar not affected.	
6	M.	32	Duodenal ulcer	100	Sc.	110	160	50	60	60	Dev. at P.	None observed.	
7	M.	30	Duodenal ulcer	100	0	92	140	48	74	60	Inc. at apex	Nervous and vomited.	
8	M.	40	Pleurisy	100	Sc.	95	140	45	72	60	Dev. at base	None observed.	
9	M.	24	Aortic regurgitation	100	Sc.	125	170	45	84	62	Inc. at base and apex	No symptoms, but developed cardiac arrhythmia 6 hours later.	
10	M.	19	Diabetes	100	0	115	160	45	64	62	Dev. at P. and apex	Basal metabolism increased.	
11	M.	30	Duodenal ulcer	90	Sc.	105	145	40	80	60	Dev. at P. and apex	Fluoroscope showed marked ventricular pulsations.	
12	M.	30	Duodenal ulcer	100	0	95	135	40	92	84	Inc. at A.	Palpitations.	
13	M.	26	Acute rheumatic fever	100	Sc.	115	155	40	68	64	Dev. at all areas	Vital capacity unchanged. Felt better and stronger.	
14	M.	21	Gastric neurosis	100	0	95	135	40	60	54	Dev. at all areas	Slight throbbing throughout body.	
15	F.	43	Pyonephrosis	100	Sc.	90	130	40	76	64	Basal metabolism increased.	
16	M.	30	Duodenal ulcer	100	Sc.	100	135	35	76	64	Urine output increased.	

17	M.	14	Rheumatic valvulitis	100	Sc.	116	150	34	88	60	Inc. at all areas; diast. at base inc.	Heart sounds stronger. Slight palpitation. Spots of erythema over anterior chest.
18	M.	60	Cerebral thrombosis	50	Sc.	130	160	30	72	66	No change	Slight headache. Heart sounds irregular in force.
19	M.	35	Normal	100	Sc.	110	140	30	60	60	Dev. at apex	Slight headache, urinary output increased, slight albuminuria.
20	M.	14	Rheumatic valvulitis	100	Sc.	115	145	30	68	60	Inc. at all areas; diast. at base inc.	Nervous after 4 hours.
21	M.	21	Gastric neurosis	100	0	95	125	30	60	60	Dev. at all areas.	None observed.
22	M.	22	Rheumatic fever	50	0	95	124	29	64	76	Inc. at all areas, dev. diast. at base	Comfortable.
23	F.	16	Gastric neurosis	100	0	105	132	27	72	72	Dev. at all areas	Fluoroscope showed marked ventricular pulsations. Nervous.
24	M.	36	Addison's disease	100	0	84	110	26	88	112	None	Heart sounds stronger. Hicough of a week's duration ceased on second day. General condition improved.
25	M.	61	Gastric neurosis	75	Sc.	120	145	25	92	68	Dev. at A. and apex	Felt better.
26	M.	64	Prostatic hypertrophy and myocarditis	50	0	95	120	25	90	86	Palpitations few minutes after injection.
27	M.	35	Pyloric stenosis	100	Sc.	105	130	25	88	96	None	None observed.
28	M.	22	Rheumatic fever	60	Sc.	115	140	25	92	100	Inc. at all areas, dev. diast. at base	Nervous after one hour.
29	M.	11	Diabetes	60	Sc.	108	130	25	96	72	Dev. at P. and apex	None observed.
30	M.	36	Addison's disease	100	Sc.	75	98	23	92	108	Nervous after one hour.
31	M.	11	Diabetes	60	Sc.	108	130	22	96	72	Dev. at P. and apex	None observed.
32	F.	29	Addison's disease	75	Sc.	90	112	22	80	68	None	Heart sounds stronger. Not consciously disturbed.
33	M.	61	Gastric neurosis	100	Sc.	140	162	22	60	60	Dev. at all areas	Gastrointestinal roentgen-ray study showed no unusual features. Thumping in chest.
34	F.	41	Arthritis deformans	100	0	90	110	20	88	88	Dev. at P.	Skin moist.
35	M.	71	Heart block	100	Sc.	90	110	20	40	58	None.	Electrocardiograms showed increase in ventricular rate.

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No.	Sex.	Age.	Clinical diagnosis.	Ephedrin administered.		Systolic blood pressure in mm. Hg.				Pulse rate.		Systolic murmurs.	Special effects.
				Amount in mg.	Method.	Before.	After.	Maximal increase.	After.	Before.	After.		
36	M.	11	Diabetes	100	O	100	120	20		72	68	Dev. at A.	Urine increased.
37	M.	14	Pneumothorax	50	Sc.	100	120	20		120	128	None	None observed.
38	F.	29	Addison's disease	100	O	90	108	18		100	90	None	None observed at time but nervous and vomited after 10 to 12 hours.
39	M.	36	Addison's disease	100	O	75	92	17		88	92	None	None observed.
40	M.	64	Chronic myocardial disease	75	Sc.	145	160	15		100	112		
41	F.	35	Endocrine disease	90	Sc.	95	110	15		88	108	None	Heart sounds louder.
42	M.	19	Convalescent pneumonia	100	Sc.	115	130	15		100	72	Inc. at all areas	Slight palpitation.
43	M.	14	Convalescent pneumonia	100	O	100	115	15		116	112	Dev. at apex	Vital capacity increased 150 cc.
44	M.	29	Retropertoneal sarcoma	100	O	115	130	15		74	64	Dev. at P.	Heart sounds stronger. Vomited but not certainly due to drug.
45	F.	29	Addison's disease	100	Sc.	90	105	15		84	68	None	Blood sugar and blood calcium not definitely affected.
46	M.	39	Syphilitic endocarditis	100	Sc.	120	135	15		98	100	Inc. at all areas, diast. at base inc.	Throbbing in head, nervous, no effect on urinary output, but albuminuria.
47	M.	39	Normal	100	Sc.	115	130	15		80	72	Dev. at apex	Comfortable but pulsus alternans developed.
48	M.	60	Cerebral thrombosis	100	Sc.	135	150	15		84	88	No change	
49	M.	30	Duodenal ulcer	100	O	105	120	15		100	88		

50	M.	22	Neurasthenia	100	0	110	124	14	72	100	Inc. at all areas	Nervous and weak.
51	M.	36	Pneumonia	50	0	115	128	13	124	124	None	None observed.
52	M.	60	Asthma	100	Sc.	110	122	12	88	88	No change	No effect on urinary output.
53	F.	16	Gastric neurosis	75	0	120	132	12	80	68	Dev. at all areas	Fluoroscope showed increased ventricular pulsations. Urine not increased
54	F.	29	Neurasthenia	100	0	115	125	10	88	80	Inc. at all areas	None observed.
55	M.	29	Arthritis deformans	1 cc adrenalin	Sc.	130	140	10	92	92	Dev. at all areas	Slight palpitation.
56	M.	36	Pneumonia	75	Sc.	105	115	10	64	72	Dev. at P.	Heart sounds stronger.
57	M.	65	Asthma	100	Sc.	110	120	10	88	88	No change.	Heart sounds irregular in force and few extra systoles. More comfortable.
58	M.	65	Asthma	50-6th hour	Sc.	No definite sustained improvement after 10 days.
59	M.	13	Diabetes	100	Sc.	110	118	8	98	100	None	Increase in amount of urine.
60	M.	26	Gastric neurosis	100	0	95	100	5	68	70	None	No effect on urinary output.
61	F.	22	Urticaria	100	0	80	95	5	None	Itching relieved. No obvious effect on lesions.
62	M.	60	Cerebral thrombosis	50	Sc.	120	125	5	76	68	No change	None observed.
63	F.	41	Arthritis deformans	50	0	100	105	5	92	104	None	None observed.
64	M.	61	Gastric neurosis	100	Sc.	140	162	5	60	60	Dev. at all areas	Gastrointestinal roentgen-ray study showed no unusual features. Thumping in chest.
65	F.	38	Addison's disease	125	Sc.	90	95	5	80	80	None	Slight dizziness.
66	M.	36	Aortic regurgitation	100	0	120	125	5	96	96	Diast. at base unchanged	None observed.
67	M.	65	Asthma	50	Sc.	120	124	4	104	100	No change	Felt better. Wheezing less and cough looser.
68	M.	38	Asthma	100	Sc.	92	95	3	118	110	None	More comfortable for 2 to 3 hours.
69	M.	44	Luetic myocarditis with fibrillation	50	Sc.	110	112	2	80	68	No change	None observed.
70	F.	29	Neurasthenia	100	Sc.	118	120	2	94	76	Inc. at all areas	Hands cold and moist.
71	M.	13	Rheumatic fever	50	0	100	100	0	74	80	No change	None observed.

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No.	Sex.	Age.	Clinical diagnosis.	Ephedrin administered.		Systolic blood pressure in mm. Hg.		Pulse rate		Systolic murmurs.	Special effects.
				Amount in mg.	Method.	Before.	After.	Maximal increase.	Before.	After.	
72	F.	34	Toxic adenoma of thyroid	100	O	135	135	0	128	128	Nervous.
73	M.	39	Syphilitic endocarditis.	50	Sc.	170	170	0	80	84	None observed.
74	M.	50	Lymphosarcoma of neck	50	Sc.	120	120	0	88	84	None observed.
75	M.	60	Asthma	100	O	105	105	0	80	90	Quite comfortable. Slight decrease in urinary output.
76	M.	36	Aortic regurgitation	100	O	115	115	0	88	96	No effect on urinary output.
77	F.	39	Neurasthenia	75	O	130	130	0	80	100	Slight increase in urinary output.
78	M.	15	Pneumonia	60	Sc.	110	105	-5	112	100	None observed. Fell asleep.
79	M.	65	Asthma	100	Sc.	120	110	-10	92	92	Heart sounds irregular in force. Wheezing less. Felt better.
80	M.	50	Lymphosarcoma of neck	75	Sc.	120	110	-10	86	94	Heart sounds louder. Sense of constriction in upper chest.
81	F.	46	Asthma	100	Sc.	132	120	-12	Attack relieved, some rales persisted.
82	M.	60	Asthma	50	Sc.	120	105	-15	108	100	Felt better. Slight tremor. Breathing easier.
83	M.	60	Asthma	50-6th hour	Definite improvement which was maintained.
84	M.	22	Gonorrheal arthritis	100	Sc.	110	90	-20	96	100	Blood sugar not affected.

(c) *Effects on Heart Action.* It was found by Chen and Schmidt, using the myocardiograph, that in dogs and cats the amplitude of the cardiac contractions is increased by ephedrin, due to stimulation of the cardiac accelerator ganglia plus stimulation of the terminals of the sympathetic nerve fibers in the heart muscle. That a similar effect is produced in man is evidenced by the observation of 3 of the patients under the fluoroscope before and after administering the drug. The excursion of the ventricular and also the aortic shadows was greater after the ephedrin had been given (observations by Dr. Eugene Pendergrass). This action was also indicated by a more forceful apex impulse which could be seen and felt, and by an increased loudness of the heart sounds. In addition it is suggested that the palpitations which were sometimes complained of may have been due to such an increase in amplitude and perhaps strength of the cardiac contractions.

An interesting finding in this connection was the development or intensification of systolic heart murmurs while the patients were under the influence of the drug. These sometimes developed at the apex alone, again at the base alone, either aortic or pulmonary area, and in other instances at all these areas. In 1 case in which 1 cc of 1 to 1000 epinephrin chlorid solution was given subcutaneously similar systolic murmurs were produced. It is important to note that these murmurs sometimes developed when the increase in systolic pressure was only slight or moderate. The explanation is not clear, but it is suggested that the basal ones may be due to a relative stenosis of the aortic and pulmonary valves resulting from unusual distension of the two great arteries at the beginning of systole and that the apical one may be due to relative insufficiency of the mitral valve from a similar distension of the heart cavities. Thayer⁶ has given such an explanation for the common functional systolic murmurs. Furthermore, it fits in well with the fluoroscopic evidence of increased contraction in systole and distention in diastole. This matter deserves further investigation.

(d) *Effects on Urinary Secretion.* In Table II are collected the hourly outputs of urine in 25 patients who were observed for five hours or more. Twenty-two of them were given ephedrin and the other 3 were used as controls. In each instance the bladder was emptied at 7 o'clock in the morning, nothing having been taken by mouth since the previous evening, and subsequently collections were made at hourly intervals until noon. In all but 1 case (No. 19) 100 cc of water were given at 7, 8, 9, 10 and 11 o'clock: in that single instance 150 cc were so given. At 9 o'clock after the second hourly collection the ephedrin was administered. The first 2 specimens, therefore, represented the output without the drug and the next 3 the output while the individuals were under its influence. Averages from these two groups were made and their relation is expressed in the ratio column. From these ratios it will be observed that the

TABLE II.—SUMMARY OF DATA ON THE EFFECT OF EPHEDRIN ON THE SECRETION AND CHARACTER OF THE URINARY OUTPUT IN 25 CASES.

No.	Sex.	Age.	Diagnosis.	Ephedrin.		Maximal systolic blood pressure increase in mm. Hg.	Urinary output.					Ratio between the hourly average before and after ephedrin.	Maximal albumin 1-6 hours after ephedrin.
				Amount in mg.	Method of administration		7 to 8 A.M.	At 9 A.M.	At 10 A.M.	At 11 A.M.	At noon.		
3	M.	22	Arthritis deformans	100	0	58	25	45	50	30	90	10:16	○
4	M.	16	Convalescent pneumonia	100	Sc.	50	60	70	150	10:8	++
8	M.	40	Pleurisy	100	Sc.	45	110	110	50	60	40	10:5	+++
9	M.	24	Aortic regurgitation	100	Sc.	45	200	170	110	220	250	10:10	+++
10	M.	19	Diabetes	100	0	45	90	310	225	310	150	10:12	++
14	M.	21	Gastric neurosis	100	0	40	30	60	50	20	60	10:10	+++
19	M.	35	Normal	100	Sc.	30	130	140	305	102	500	10:22	+
29	M.	11	Diabetes	100	0	22	50	50	150	250	150	10:36	++
37	M.	14	Convalescent pneumonia	100	0	20	60	20	180	50	85	10:24	+++
44	M.	29	Retropertoneal sarcoma	100	0	15	60	60	80	50	80	10:11	

45	F.	29	Addison's disease	100	0	15	45	48	60	60	100	10:16	
47	M.	39	Normal	100	Sc.	15	32	20	22	21	24	10:8	+++
49	M.	30	Duodenal ulcer	90	Sc.	15	50	145	350	150	100	10:20	
52	M.	60	Asthma	100	Sc.	12	70	60	60	60	50	10:9	O
53	F.	16	Gastric neurosis	75	0	12	25	30	20	20	20	10:8	
59	M.	13	Diabetes	100	Sc.	8	12	70	160	340	200	10:57	
60	M.	26	Gastric neurosis	100	0	5	50	50	50	45	46	10:9	
64	M.	61	Gastric neurosis	75	0	5	50	50	150	200	100	10:30	+++
66	M.	36	Aortic regurgitation	100	0	5	100	120	110	75	90	10:8	
75	M.	60	Asthma	100	0	0	90	50	30	50	50	10:6	
76	M.	36	Aortic regurgitation	100	0	0	90	80	80	48	45	10:7	
77	F.	39	Neurasthenia	75	0	0	15	15	20	25	30	10:17	O
Controls	F.	16	Gastric neurosis	None	25	20	25	25	25	10:11	
	M.	61	Gastric neurosis	None	60	25	50	50	40	10:11	
	M.	40	Pleurisy	None	60	60	50	70	60	10:10	

results are conflicting and not at all in agreement with the effect on blood pressure, as was expected. Usually there was an increase in output and this was very marked in some, especially in two diabetics (Nos. 29 and 59), yet another diabetic (No. 10) showed a ratio of only 10 to 12. In 2 instances (Nos. 19 and 47) the experiment was continued over a period of ten hours but with different results, one showing a decided diuresis (10 to 22) and the other a slight decrease (10 to 8) for the three-hour period immediately following the injection. The later collections were the average ones for the pre-ephedrin period. In connection with these 2 individuals, both of whom were presumably normal, it is interesting that one averaged only 26 cc of urine per hour on 100 cc of water while the other put out an average of 135 cc hourly on an intake of 150 cc on the three controls (Nos. 74, 75 and 76) the ratio showed no difference between the outputs in the two periods.

These varying results lead to no definite conclusion, but seem to show a tendency to diuresis after ephedrin administration. The work of Chen and Schmidt indicated that the drug caused first a decrease in output from renal vasoconstriction and that this was followed by a diuresis incident to a secondary vasodilatation while the general blood pressure was still elevated. The differences in the effects on the urinary secretion might, therefore, be due to variation in the relation between the ephedrin effect on the general blood pressure and on the renal vascular apparatus.

It has been suggested that there might be in addition some renal irritation which aided in the diuresis. This thought was based on a single observation by Chen and Schmidt in a rabbit which showed a diuresis with intermittent glycosuria and albuminuria after excessive intravenous doses daily for nine days. In spite of perfect health and a gain in weight during the next twelve days, it showed at the end of that time, when killed, some degenerative changes in the convoluted tubules. Rabbits, however, frequently develop tubular lesions spontaneously, and a single case of such a change in a rabbit is, therefore, of no significance. Furthermore, in all the clinical cases that have been studied no evidence of disturbance in either the quantity or the character of the urine lasting longer than a few hours has been observed.

A consideration of the influence of the drug on the character of the urine is not to be dealt with extensively here, in as much as Dr. Isaac Starr expects to report on this separately, but the last column in Table II, supplied by him, shows some albuminuria for a few hours after ephedrin in most of those patients who had a decided increase in blood pressure. *This again does not prove renal irritation*, for work recently accomplished in the laboratory of pharmacology of this university indicates strongly that transient albuminuria may result from the renal vasconstriction produced by epinephrin (and presumably by other substances of the same type),

not because of a direct damaging action upon renal tissue but because of transient cessations of circulation through the blood-vessels of such duration as to cause the alterations in permeability characteristic of asphyxia.

(e) *Effects on the Basal Metabolism and Blood Sugar.* Basal metabolism studies before and after the administration of ephedrin are being made by Dr. Leon Jonas and the writer. These also will be reported separately but the following table is given to show the decided increase that has occurred in 2 of 4 cases. The same investigators are studying the blood sugar effects, but as yet have got entirely negative results.

TABLE III.—EFFECT OF EPHEDRIN ON THE BASAL METABOLISM IN 4 CASES.

No.	Sex.	Age.	Amount of ephedrin administered subcutaneously.	Maximal systolic blood pressure increase.	Basal metabolism before, and a half hour after ephedrin.	
					Before.	After.
9 . .	M	24	100 mg.	45	+6	+21
10 . .	M	19	100 mg.	45	-15	+7
85 . .	F	27	100 mg.	25	-7	+2.3
24 . .	M	36	125 mg.	20	+4	+9

IV. *Special Clinical Observations.* The following cases are reported to show in greater detail the results obtained from the therapeutic use of ephedrin in certain types of disease in which, on account of its physiological actions, there was reason to believe that this drug might be of practical value. It is appreciated that the number of cases in each group is too small to justify final conclusions but it is felt that they are of sufficient significance to be reported and that they warrant further studies in such and other clinical conditions.

A. *Addison's Disease.* It could hardly be expected that any drug would serve as a cure for a disease that is dependent upon extensive destructive change in such important glands of internal secretion as the adrenals. Furthermore, it is known that injections of epinephrin itself have had little or no influence on the symptoms or course of Addison's disease. Yet it is appreciated that it has been impossible practically to produce an epinephrin effect continuously in patients because of its brief action and the necessity of giving it hypodermically. These practical objections being overcome in ephedrin, which has similar physiological actions, it seemed worth while, and especially so in view of Chen and Schmidt's encouraging report in a single case, to try it out in other cases of Addison's disease with the hope that at least in the early ones it might compensate to some extent for the deficiency in adrenal function. The results are not highly encouraging but do seem to

suggest that at least temporary benefit may be expected in some cases.

Case Reports. CASE I.—A married woman, aged twenty-nine years, a private patient, was admitted to the University Hospital on October 16, 1924, complaining of weakness, loss of weight and a brownish discoloration of the skin. She had been losing weight for five months (170 down to 126 pounds). The brownish tint of the skin had developed insidiously, being first noted under the eyes and under the chin. When I first saw her, the whole skin surface seemed somewhat discolored, and especially was this marked over the face, arms, hands, back and upper anterior chest. There were definite discolorations of the flexor and extensor surfaces of the joints and of the umbilicus and nipples. There were also spots of blackish pigmentation along the dorsum of the tongue. The vagina showed brownish-black spots. The heart and lungs were negative to physical examination and no signs of gastrointestinal disease could be found. The blood pressure was 90 systolic and 65 diastolic. The blood counts and urinalyses were negative. A roentgenological examination of the chest was negative except for some calcified glands about the root of right lung. Other laboratory examinations, including a roentgenological study of the gastrointestinal tract, gastric analysis, feces examination and a van den Bergh test were negative. A von Pirquet test was positive. A blood-sugar tolerance test showed a quick response with a secondary drop to an unusually low level (49 mg. after one and a half hours).

On an initial dose of 50 mg. of ephedrin hypodermically her systolic blood pressure rose from 92 to 105 mm. of mercury and her pulse rate dropped from 72 to 50. No change in the blood-sugar level occurred (see Table IV).

TABLE IV.—EFFECT OF 50 MG. EPHEDRIN, GIVEN SUBCUTANEOUSLY, ON BLOOD PRESSURE, PULSE RATE AND BLOOD SUGAR LEVEL IN A CASE OF ADDISON'S DISEASE.
DRUG GIVEN AT 9 A.M.

	Time of day.					
	9 A. M.	9.30 A.M.	10 A. M.	10.30 A. M.	11 A. M.	11.30 A. M.
Blood pressure in mm. Hg.	92/60	100/65	105/65	103/65	106/65	100/65
Pulse rate	72	60	50	54	56	60
Blood sugar in mg. per 100 cc	85	86	84	85	84	

After each of several similar doses of ephedrin given both orally and hypodermically she complained of some nervousness, a feeling

of excitement or apprehension, and a few times a little tremor of the hands was noted. The dose was therefore reduced to 25 mg. three times a day and on this she was discharged from the hospital to her home in another part of the state. The supply of the drug lasted only two or three weeks longer but during that time she improved in strength considerably and was able to take up her work again. Then, without the medicine, her weakness returned. From January 25 to February 10, on 30-mg. doses three times a day she again showed symptomatic improvement, but by February 24 her weight had dropped to 111 pounds and her general condition was no better. Then several acute experiments with ephedrin were made. It was found that a hypodermic dose of 75 mg. raised the systolic pressure from 90 to 110 mm. of mercury and did not disturb the patient so much as the 50 mg. doses had done before. On 100 mg. her blood sugar was not affected; neither was her blood calcium or phosphorus. After that, she took the medicine only for a period of ten days, because of our inability to furnish it, but during that time she gained 4 pounds in weight, felt better and was able to be out of doors and reasonably active. On April 14, she weighed only 105 pounds and her blood pressure was 95 systolic and 65 diastolic. Again she was started on 50-mg. doses orally three times a day. This soon caused nausea and vomiting and had to be abandoned.

The symptomatic improvement during the short periods when ephedrin was being given and the gain in weight over one period of ten days as well as the positive increase in blood pressure for three to five hours after single doses indicate that it was of at least temporary value in this case. It is hoped that by using smaller doses in the future the patient's unfavorable reactions may be avoided and that she may be kept continuously under its influence.

CASE II.—A man aged thirty-six years, was admitted to the University Hospital with a history of attacks of weakness and gradually increasing skin discoloration over a period of five years. His skin generally and the entire mucous membrane of his mouth showed a marked brownish-black hue and his blood pressure was consistently low. There were no demonstrable visceral lesions. After careful study the diagnosis of Addison's disease was made and ephedrin studies were undertaken. On a dose of 100 mg., given subcutaneously, his blood pressure did not vary over a period of one hour, remaining at 80 systolic and 50 diastolic. His pulse rate increased from 84 to 100. A few days later with a similar dose the blood pressure went from 75 systolic and 50 diastolic to 90 systolic and 50 diastolic in thirty minutes and after three hours was 98 systolic and 50 diastolic, the pulse rate having risen from 92 to 108. Again on an oral dose of 100 mg., after having taken it routinely in 50-mg. doses three times a day for a week, the pressure

rose from 75 systolic and 55 diastolic to 92 systolic and 60 diastolic in two hours and after a slight exertion three hours later it went to 115 systolic and 75 diastolic. Then the ephedrin was omitted for thirty-six hours when 125 mg. were given subcutaneously, this causing a rise from 72 systolic and 55 diastolic to 92 systolic and 55 diastolic in thirty minutes and an increase in the pulse rate from 84 to 100. His basal metabolism before this dose of ephedrin was +4 and thirty minutes afterward it was +9. Two days later, the patient having received none of the drug in the interval, he developed an acute respiratory infection and died within twenty-four hours.

This patient had no disagreeable sensations from his doses of ephedrin, got a moderate increase in his blood pressure after each administration and was feeling stronger and better so long as it was kept up.

B. Asthma. In a single experiment on a pithed dog, after an injection of physostigmin had produced marked bronchial spasm, Chen and Schmidt secured prompt dilatation of the bronchi by ephedrin, though the effect was not well sustained and subsequent doses did not cause dilatation even when epinephrin continued to be effective. They had no opportunity to try the drug clinically, but they expected that beneficial results might be obtained. The following case reports are, therefore, of interest and seem to indicate that ephedrin does often have a relaxing influence on the bronchial spasm of asthma though this cannot be counted upon in every case and it is perhaps never as complete as that obtained from epinephrin.

CASE III.—A woman, aged sixty-six years, had suffered from an allergic type of hay fever and asthma for eighteen years. On admission to the wards of the hospital she was intensely dyspneic and cyanosed and had typical asthmatic breathing. She was relieved by injections of epinephrin several times and then put on 50-mg. doses of ephedrin by mouth four times a day. Subsequently she showed considerable improvement, although occasionally she still presented slight wheezing and once the intern gave another injection of epinephrin for a moderately severe attack during the night. On another such occasion an extra dose of 100 mg. of ephedrin by mouth gave definite relief. After that she was given 100 mg. orally four times a day and required in addition only an occasional hypodermic of epinephrin. This patient's blood pressure was carefully followed at half-hour intervals after one 50-mg. oral dose and after several 100 mg. subcutaneous doses of ephedrin. Neither the systolic nor diastolic pressure varied appreciably, indeed sometimes decreased, and yet she felt more comfortable for about three hours after these doses and her wheezing was considerably reduced.

In a personal communication Dr. Alfred Stengel gives the follow-

ing data on two of his private patients with asthma to whom he had given ephedrin.

CASE IV.—“Mrs. P., aged sixty-five years, has had asthmatic attacks for eighteen years. Under medical treatment she at one time was relieved for a period of a year, but with this exception, has suffered rather constantly. There has been some intranasal trouble and a good deal of tonsillitis; latterly, she has arthritic changes in her fingers. On examination, I found considerable evidence of sclerosis and some hypertension. The heart was not enlarged, but there was a soft systolic murmur over the arch and an accentuated second sound; lungs definitely emphysematous and musical rales everywhere. She improved somewhat under medical treatment (potassium iodid, extract of opium, digitalis and hyoscyamus), but was not very thoroughly relieved. On April 10, I gave her some of the ephedrin capsules (50 mg.) and told her to take them twice daily. She has since been in on two occasions reporting a remarkable relief from her asthmatic attacks. How much this may be due to the capsules, and how much to the capsules of cerium oxalate, digitan and belladonna that I had asked her to take at the same time, I can hardly say.”

CASE V.—“Mr. J. B. C., aged fifty-three years, began to suffer with asthmatic symptoms at about thirty-six years of age, and continued for several years. He has not had in recent years any severe attacks, but early in 1925 he consulted me on account of asthmatic breathing, and stated that he had been troubled a little for several years past. During the winter of 1924-25, after a coryza and more general upper respiratory infection, marked asthmatic symptoms occurred. Various sorts of medical treatment were more or less unavailing. In May, he began the use of ephedrin, taking 2 or 3 doses (50 mg.) daily and an occasional extra dose for the paroxysms. This had an immediate effect in reducing the violence of his paroxysms and soon made the further use of epinephrin injections unnecessary. According to reports to me, the effect of the ephedrin was very striking and unmistakable. Just before sailing for Europe on June 24, he reported that his asthma had practically ceased and that he had used but 1 capsule of ephedrin for some time past.”

CASE VI.—Dr. Richard A. Kern reported to me the case of a woman, aged fifty-four years, who had had pollen asthma and hay fever for twenty years. She had been getting 2 to 6 hypodermics of epinephrin daily. During one period of four days, on two to five 50-mg. capsules of ephedrin by mouth, no hypodermics were required, but subsequently she became nauseated from the capsules and returned to the hypodermics. Later on only 2 capsules of

ephedrin a day and 2 hypodermics of epinephrin her condition remained very good for five days of observation. There was no significant change in her blood pressure at any time.

CASE VII.—M. J. K., a patient of Dr. S. Paul Taylor of Altoona, Pennsylvania, who had suffered from severe asthmatic attacks irregularly for twenty years, was finally able to get relief only from 20 to 25 minim doses of epinephrin chlorid and this relief was far from complete. He was getting 4 such doses daily when I first saw him with Dr. Taylor. Physical examination was negative but for the signs of emphysema with asthma. Roentgenological examination of the chest suggested some bronchiectasis and bronchoscopic study by Dr. R. M. Lukens showed a chronic tracheobronchitis with a little blood-tinged pus coming from the left lower lobe bronchus. He was started on three 30-mg. capsules of ephedrin daily and later they were given as frequently as every two hours but no relief from his dyspnea ensued. On the more frequent doses he complained of "levitation, light headedness, fluttering in the chest, perspiration and an enlarged head."

In this case of severe asthma no benefit was derived from ephedrin although it was given to the point of producing toxic symptoms.

CASES VIII and IX.—Two men, sixty-five and sixty years of age respectively, had suffered from asthma for many years and both had associated emphysema with myocardial degeneration. Neither showed any marked blood-pressure increase after 50 to 100 mg. doses of ephedrin, given orally or subcutaneously, and on several occasions there was a drop in the systolic blood pressure within one to two hours after its administration. Both, however, got a certain amount of symptomatic relief for two to four hours after its use and often the cough was looser and more productive. There was also noted some decrease in the intensity of the wheezing breath sounds. At other times there seemed to be no effect on the physical signs.

These 2 patients were put on 50-mg. doses orally three times a day continuously for several weeks. One showed only slight improvement. This patient had been relieved by epinephrin injections when first admitted to the hospital, but at the time the ephedrin administrations were begun even 1-cc doses of 1 to 1000 epinephrin chlorid gave only slight relief. The other patient still got relief from epinephrin for thirty to sixty minutes, but after the ephedrin was begun he only occasionally required the hypodermics of epinephrin.

C. Other Allergic Conditions. CASE X.—A patient, a young married woman, on the private service of Dr. Alfred Stengel, having a pleurisy with effusion, developed acute urticarial lesions involving the entire body surface. An injection of 5 minims of 1 to 1000 epinephrin chlorid gave relief from the intense itching and an oral

dose of 50 mg. of ephedrin and of 50 mg. of luminal one hour later kept her sufficiently comfortable to sleep for ten hours. Then the itching returned and was not definitely affected within an hour by a second dose of 50 mg. of ephedrin, but after another dose of the same amount there was distinct relief. Within an hour after the last dose the blood pressure rose from 85 systolic and 60 diastolic to 95 systolic and 60 diastolic. Subsequently 100-mg. doses were given by mouth approximately every six hours and each time there was relief from the subjective symptoms for four to six hours. The lesions themselves were not objectively affected and did not disappear until the fourth day. At no time were any disagreeable effects from the ephedrin experienced.

CASE XI.—A boy, aged fourteen years, developed a generalized urticaria one week after a prophylactic dose of antitetanic serum. An injection of 5 minims of 1 to 1000 epinephrin chlorid solution gave complete relief for an hour or more and subsequently he was kept reasonably comfortable by 50-mg. doses of ephedrin orally four times a day. At one time during the second day his subjective symptoms were almost as marked as in the beginning and an extra dose of ephedrin at that time (three hours after the last regular dose) caused a disappearance of the lesions and the itchiness within thirty to sixty minutes.

D. Circulatory Disturbances. The predominant action of ephedrin as a stimulant to the circulation, by its effect on both the heart and the bloodvessels, suggested that its chief therapeutic value might lie in cases of marked circulatory depression, such as occurs in surgical shock, in certain cases of myocardial weakness, and in various prolonged low blood pressure conditions. It has been demonstrated how the blood pressure can be temporarily elevated by its use (see Table I) and it was hoped that a continuous blood-pressure increase might result from its administration at fairly frequent intervals over considerable periods of time, but as yet no such effect has been observed. Even in Cases I and II (Addison's disease), in which the patients' general condition seemed to improve while frequent doses were being given, it was found impossible to maintain the pressure constantly at a higher level. It is conceivable, however, that merely frequently repeated temporary elevations may be beneficial aside from any other effects that the drug may have. Case XII would seem to prove this.

CASE XII.—A man, aged sixty-five years, was admitted to the private service of Dr. Alfred Stengel in moderate cardiac decompensation and with marked distention of the urinary bladder from hypertrophy of the prostate. After his bladder had been slowly emptied over a period of several days by Dr. Alexander Randall he developed hiccough, which persisted in spite of all the usual rem-

edies for eight days. At this time his systolic blood-pressure reading was 95 mm. of mercury and his diastolic 55. He was then put on ephedrin in 50-mg. doses by mouth, three times a day, all other medication having been stopped two days before. His systolic pressure promptly rose to 112 to 120 following each injection and the diastolic proportionately. After forty-eight hours the hiccough ceased and during the next two weeks, while still getting the ephedrin, his general condition improved so much that it was considered safe to do the complete radical prostatic operation. This was accomplished under spinal anesthesia by Dr. Randall and the patient is now making an uneventful convalescence and has left the hospital.

There are other cases of a more acute nature, such as those of surgical shock and collapse, in which prompt elevation of the blood pressure for a few hours may be life-saving. Studies of the effect of ephedrin in such cases is being made by Dr. L. K. Ferguson on the neurosurgical service of Dr. Charles H. Frazier and will be reported later. What may be expected in such patients is suggested by the temporary result obtained in the following case:

CASE XIII.—A man, aged forty-two years, who had been operated upon by Dr. E. L. Eliason for an acute intestinal obstruction and who was dying of acute general peritonitis had marked cyanosis and a cold clammy skin with no radial pulse or detectable blood pressure when 100 mg. of ephedrin sulphate were injected into one of his jugular veins. Within ten minutes a systolic blood pressure of 60 mm. of mercury and a diastolic of 50 was obtained, and five minutes later it was 65 systolic and 50 diastolic. He was then given 500 cc of a 10 per cent glucose solution intravenously. At the end of an hour after the first observation the reading was 75 systolic and 40 diastolic. Almost immediately after the ephedrin was injected a radial pulse became palpable and it later grew stronger and fuller during the administration of the sugar solution. After two and a half hours the pressure began to fall (60 systolic and 45 diastolic) and a second dose of ephedrin had no appreciable effect. The patient died ten hours later.

It is believed that other less hopeless cases of this type might be carried through a critical period by such use of ephedrin. Also the cases of sudden heart failure which are often revived by epinephrin might receive a like effect from intravenous or intracardiac administrations of this drug.

The following case of heart block is included because of the very interesting results obtained and the suggestions it may have for those interested in cardiac physiology and therapeutics.

CASE XIV.—A man, aged sixty years, with myocardial disease and generalized arteriosclerosis, fell down stairs and was admitted to the surgical service of Dr. E. L. Eliason with a broken fibula and

complete heart block. His ventricular rate ranged from 34 to 42; his systolic blood pressure was 90 mm. of mercury and his diastolic 50. An electrocardiogram by Dr. Charles C. Wolferth confirmed the cardiac diagnosis. Immediately following this examination the patient was given 100 mg. of ephedrin subcutaneously and subsequent electrocardiograms and blood pressure determinations at ten-minute intervals gave the results tabulated below:

Hour.	Blood pressure.	Electrocardiographic findings.	
		Ventricular rate.	Auricular rate.
11.25 A.M.	90/50	38	110
11.35 A.M.	50	125
11.45 A.M.	110/55	Ranged from 55 to 53	125
11.55 A.M.	90/55		125
12.15 P.M.		86

On these electrocardiographic studies Dr. Wolferth reported as follows:

"The auricular rate increased from 110 to 125 within ten minutes after injection and remained at 125 for thirty minutes. Fifty minutes after injection the rate had fallen to 86. No disturbances in rhythm were noted. The shape of the *P*-waves changed very markedly.

"The ventricular rate before injection was 38 and occasionally showed slight irregularity. *A-V* dissociation was complete at all times. Ten minutes after injection the ventricular rate had risen to 50 and during the next forty minutes ranged between 50 and 53. The rhythm at this time was regular. Changes were noted from time to time in the shape of the ventricular complexes."

These findings indicate a definite influence of ephedrin on both the ventricles and auricles of the heart when they are acting independently of each other. These effects may be due to stimulation of the cardiac accelerator ganglia or the sympathetic nerve endings, or both, or they may be due to direct action on the heart muscle. These matters will be discussed by Dr. Wolferth and the writer in a subsequent publication when other cases have been studied.

V. Effects on the Nasal Mucous Membrane. Among other studies on ephedrin which have been undertaken in this institution is that of the effect of its local application on the nasal mucous membrane by Dr. George Fetterolf and Dr. Marshall B. Sponsler. Their paper is now in the hands of the publishers but they permit me to report that a 5 per cent solution of ephedrin sulphate painted lightly on the mucous surface with a brush caused definite contraction in every one of 17 cases within a few seconds to one minute, the maximal contraction occurring in an average of two and one-third minutes, that the contraction was marked throughout the entire extent of the turbinate even when the drug was applied to only a limited portion of the anterior end and that the lower border was

so contracted as to give the appearance of being drawn upward. The mucosa became so thin and flat that it fit the bones as a glove fits the finger. The color was invariably altered to a paler hue, but there was never the extreme pallor seen with epinephrin. The first evidence of relaxation appeared on an average of two hours and thirty-five minutes after the ephedrin was applied. Finally, and of extreme importance, was the discovery that in none of the cases did there occur any evidence of irritation such as occurs with epinephrin.

This work, therefore, suggests certain distinct advantages of ephedrin over epinephrin in the local treatment of nasal conditions. Its freedom from secondary irritation and the duration of its constricting action suggest that it might also be of value in otolaryngological surgery. Credit for the thought of so using ephedrin locally in the nose belongs to Drs. Alice H. Cook and Otto Willner of Peking, China, who made the suggestion to Dr. Schmidt.

It has been proposed that ephedrin solution might be of equal or even greater value if used as a nasal spray. Such a form of application could be handled by the patient himself and might for that reason be of extreme value in certain local conditions, such as hay fever and acute sinus conditions, which require a more or less continuous effect. This method of applying the drug is now being tried out in our medical wards and will be reported upon at another time.

VI. Conclusions. 1. Ephedrin has general physiological effects in man similar to those produced by epinephrin. It has, however, distinct practical advantages over epinephrin because of its more prolonged action and the fact that it can be administered effectively by mouth.

2. In doses of 50 to 125 mg., given orally or subcutaneously, ephedrin sulphate usually raises the systolic and diastolic blood pressure and decreases the pulse rate for a period of several hours. It also stimulates the heart action and has a tendency to increase the output of urine. It sometimes increases the basal metabolism.

3. Its administration caused temporary improvement in 2 cases of Addison's disease, gave relief in the paroxysmal attacks of certain cases of asthma, relieved the subjective sensations in a case of urticaria, caused a disappearance of urticarial lesions in a case of serum disease, and produced marked temporary improvement in a case of circulatory collapse and steady and continuous improvement in a case of circulatory failure incident to myocardial disease and the evacuation of an overfilled urinary bladder.

4. In a single case of complete heart block it produced an increase in both the auricular and the ventricular rates and caused alterations in the character of the electrocardiographic tracings.

5. Locally applied to the nasal mucous membrane, ephedrin causes prompt contraction which persists for more than three hours and has no local irritant effect.

6. It is believed that the widest range of usefulness of ephedrin will be found in the treatment of asthma and of acute circulatory depression, and in the management of certain congestive nasal conditions.

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ONE HUNDRED CONSECUTIVE CHOLECYSTECTOMIES.

A BACTERIOLOGICAL AND HISTOLOGICAL STUDY OF GALL BLADDER LESIONS TOGETHER WITH A HISTOLOGICAL STUDY OF THE ASSOCIATED APPENDICES.

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THE primary purpose of this study was to determine the relation between histologically pathological gall bladders and the organisms that can be cultured from their fluid contents.

The cases in this group were included among operations performed by five surgeons at the Lakeside Hospital and the Cleveland Clinic Hospital from 1922 to 1924, no selection of the cases being made.

The study was suggested by the belief expressed by many writers, that organisms are always present in the fluid content of all pathological gall bladders. Our purpose, therefore, was not to prove that the isolated organisms produced the lesions in the gall bladder, but merely to determine in what percentage of cases organisms are present in the fluid contents in histologically pathological gall bladders, and the relative frequency of occurrence of different types of organisms.

In none of the cases in which the bacteria were isolated was the fluid content of the gall bladder normal. In nearly all of these there was a definite increase in the amount of mucus, together with a few pus cells and epithelial cells. In 12 instances the gall bladder contained sand without any definite stone formation.

In 3 cases "white bile" was present and in 6 others the gall bladder contained practically no fluid content. In some only a slight amount of mucus with pus cells and a few epithelial cells was obtained, the gall bladders being nearly filled with stones,

In every case the bile was obtained aseptically immediately after removal of the gall bladder and was inoculated within a half hour upon 1 per cent bouillon, blood agar and Endo's medium and incubated at 37° C.

No dilutions of the bile were made in order that the growth obtained might represent, as nearly as possible, the organisms present in a concentration of bile identical with that in the gall bladder.

More positive cultures were obtained from the bouillon media than from any of the other media used. This bears out the study made by Drennan,¹ which showed that bacteria will not grow satisfactorily if more than a 70 per cent concentration of bile is present. The highest percentage of growth was secured from the clearest bile and from that which contained the smallest percentage of bile salts.

The cultures were considered sterile if after a lapse of seventy-two hours no growth was found on any of the media.

For the histological examinations the sections were prepared by fixation in formalin, after which the tissues were mounted in paraffin, being stained after sectioning with eosin and hematoxylin. The histological diagnoses were made by three pathologists. From the available material the following data have been compiled:

The 100 cases studied included 84 females and 16 males. The average age of the females was forty-one years and of the males forty-six years, the youngest being twenty-three years and the oldest seventy-one years of age; 69 of these patients had been married and 57 per cent of the women had borne one or more children; 1 woman had had eleven children.

The average duration of illness prior to the operation, as indicated by the onset of the first definite symptoms, was six and a half years. The shortest duration was three hours and the longest thirty-six years, 1 case having had forty-eight definite attacks prior to operation. Ninety-six patients gave a history of nausea and vomiting. The attacks began at night in 48 cases. Belching or eructation of gas was present in 88 cases. There had been one or more distinct attacks of jaundice in 12 cases; 1 patient had had three attacks before operation, and 3 came to operation with obstructive jaundice. In 71 instances epigastric pain radiating to the back was experienced during the attacks, and in only 46 was there a definite history of pain radiating to the right shoulder—a lower incidence of this symptom than is generally believed. Only 12 patients gave a history of having had typhoid fever. In practically all of the cases there was a history of constipation or costiveness of the bowels. In 8 patients a previous cholecystostomy had been performed.

¹ A Bacteriological Study of the Fluid Contents of One Hundred Gall Bladders Removed at Operation, *Ann. Surg.*, 1922, 76, 482.

In 9 instances the roentgen-ray films gave positive evidence of stones, and in 6 others a tentative diagnosis of gall bladder disease was made from the roentgenogram.

In practically all of the cases the operation was performed under nitrous oxid-oxygen and local anesthesia with novocain, with the addition of 5 to 25 per cent ether for from two to thirty-five minutes while the exposure and deep dissection were being made. In 22 cases ether was not used. The average duration of anesthesia was sixty-three minutes, the longest period being one hundred and thirty-six minutes.

The primary incision was right rectus in 86 cases, pararectus in 10 and transverse epigastric in 4 cases.

In 58 instances the gall bladder was dissected from the cystic duct toward the fundus of the gall bladder, the cystic duct and artery being separately ligated in every case. In 86 of the cases the cystic duct was doubly ligated, proximal to the common duct with catgut, and distal to this ligature with silk.

In practically all of the cases in which there were adhesions the adhesions were dissected free and the gall bladder was dissected from the fundus toward the cystic duct. In 15 cases the serosa was sutured over the gall bladder bed to check oozing.

In 99 instances drainage was obtained by from one to three cigarette drains. In 2 cases there was drainage of bile which in 1 persisted for sixteen days and caused a necrotic slough of the subcutaneous tissue in the right hypochondrium. In 8 cases drainage was established through the flank by the insertion of cigarette drains through a stab wound below the costal margin. The drains were removed in from six to eight days.

Two cases were complicated by the presence of stones in the common duct, the typhoid bacillus being isolated in 1 of these. In 3 patients the gall bladder contained "white bile," and in 2 of these stones were impacted in the cystic duct.

The operative notes in 13 instances mention enlargement of the periductal glands and scarring and cirrhotic changes in the liver in the gall bladder region. In 4 cases it is stated that the pancreas was enlarged and hard.

The hospital period varied from three to forty-seven days, the average period being eighteen and a half days.

The operative mortality in this series was 3 per cent, the causes of death being respectively pneumonia, acute dilatation of the heart with acute edema of the lungs, and acute nephritis superimposed upon a chronic nephritis. In 3 cases there was an acute suppression of urine, which in 2 cleared up after the second day.

The gross description of the gall bladder specimens mentions adhesions on the gall bladder wall in 41 cases; a definite increase of the fat deposit in the gall bladder wall in 28; thick, tenacious, dark green bile containing a large amount of mucus in 47, and thick gall bladder walls in 31.

The stones varied greatly in size, shape and consistency, being described as soft crumbly sand in 11 cases; in 1 instance seventy-eight stones were present.

TABLE I.

Patient.	No.	Average age in years.	Average duration symptoms, years.	Infected fluids.	Sterile fluids.	Cholecystitis with stones.	Cholecystitis without stones.
Women . . .	84	41	8½	24	60	52	32
Men . . .	16	46	4	8	8	10	6

The bacteriological study of the fluid contents of these gall bladders showed positive cultures in 32, these being pure cultures of *B. coli* in 18, staphylococcus and *B. coli* in 2 cases and streptococcus or staphylococcus or both in 11; in 1 patient the *B. typhosus* was isolated. (See Table II.)

TABLE II.—DIAGNOSIS ASSOCIATED WITH DIFFERENT TYPES OF GALL-BLADDER LESIONS AS DETERMINED IN A STUDY OF ONE HUNDRED CASES.*

Type of lesion as histologically determined.	<i>Bacillus coli.</i>	<i>Staphylococcus aureus.</i>	<i>Streptococcus.</i>	<i>Staphylococcus albus.</i>	<i>Typhoid bacillus.</i>	<i>Bacillus coli</i> and <i>staphylococcus.</i>	<i>Streptococcus</i> and <i>staphylococcus.</i>	Sterile.	Total.
Acute cholecystitis without stones . . .	2	1	..	1	4
Acute cholecystitis with stones . . .	1	1
Acute and chronic cholecystitis with stones . . .	2	1	5	8
Chronic fibrous cholecystitis without stones . . .	3	1	1	..	30	35
Chronic fibrous cholecystitis with stones . . .	7	3	..	1	27	38
Subacute cholecystitis with stones	2	1	..	3
Subacute and chronic cholecystitis	3	3
Empyema of gall bladder	1	..	1
Hydrops of gall bladder	1	1
Subacute and pericholecystitis . . .	2	1	1	4
Normal gall bladder . . .	1	1	2
Total . . .	18	7	1	1	1	2	2	68	100

* The diagnosis as stated is based on the histological findings, the presence of stones being added to the histological findings in the cases in which they were present.

In 52 of these patients an appendectomy was performed together with the cholecystectomy. The histological diagnosis in each of

these has been tabulated together with that of the associated gall bladder. (Table III.)

TABLE III.—TYPES OF LESIONS OF THE APPENDIX ASSOCIATED WITH VARIOUS TYPES OF GALL BLADDER LESIONS IN FIFTY-TWO CASES.*

	Chronic fibrous appendicitis.	Obliterative appendicitis.	Peri-appendicitis.	Acute appendicitis.	Subacute appendicitis.	Normal appendix.	Total.
Acute cholecystitis without stones . . .							
Acute cholecystitis with stones . . .							
Acute and chronic cholecystitis with stones	1	1	2
Chronic fibrous cholecystitis without stones	10	9	2	..	1	2	24
Chronic fibrous cholecystitis with stones .	5	7	1	4	17
Subacute cholecystitis with stones . . .	1	1	2
Subacute and chronic cholecystitis (gastrectomy tube)	1	1	2
Empyema of gall bladder	1	1
Hydrops of gall bladder	1	..	1
Subacute and pericholecystitis	1	..	1
Normal gall bladder . . .	1	1	..	2
Stone in cystic duct . . .							
Total . . .	19	18	3	1	4	7	52

* The type of lesion of both the gall bladder and the appendix was determined in each case by histological examination.

Conclusion. 1. Organisms were cultured from the fluid contents of pathological gall bladders in less than one-third of the cases in this series.

2. *B. coli* was the predominating organism in the positive cultures.

3. The highest percentage of positive cultures was obtained from the gall bladders which contained the lowest percentage of bile salts.

4. Even after double ligation of the cystic duct there was an escape of bile in 2 cases, a finding which reinforces the argument for drainage of the abdomen after cholecystectomy.

5. Histological changes seem to indicate that the lesions in the appendix are of longer duration than the other associated gall bladder lesions.

6. Histologically pathological gall bladders with culturable organisms in their fluid content have a far higher mucus content than normal gall bladders. The walls show an increase in fat content and thickening.

A REVIEW OF TWENTY-EIGHT CASES OF PURPURA HEMORRHAGICA IN WHICH SPLENECTOMY WAS PERFORMED.*

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THE recommendation of splenectomy in the treatment of cases of hemorrhagic purpura is based on the apparent importance of the reduced number of platelets and their morphologic abnormality, together with the accumulated data which showed an increase in the number of platelets following splenectomy in experimental animals and also in man when operation has been performed for other conditions. The good temporary effect of radiation of the spleen in hemorrhagic diseases in general is a contributing consideration.

This paper, which has been prepared in the hope that it may be valuable for reference, consists of a review of 28 cases in which splenectomy has been performed for purpura hemorrhagica. Nineteen of the cases have been reported in the literature, 8 have been previously reported from the Mayo Clinic, and 1 other case from the Clinic has not been previously reported. Short abstracts of all of the cases, and a summary of the various features are presented.

Abstract of Cases. CASE I.—Kaznelson's first case was that of a woman, aged thirty-six years, who had had petechiæ and purpuric areas since childhood. In the preceding ten years she had had three severe attacks of hemorrhagic purpura, the erythrocytes on one occasion dropping to 940,000. During a remission in 1910 the patient had given birth to a child, apparently without incident. At the time of splenectomy the erythrocytes numbered 3,100,000, the leukocytes 2760 and the platelets 600, many of which were of the giant form. A few myelocytes and normoblasts were present in the smears. The spleen was palpable.

Splenectomy was performed in 1916. A few days after operation the platelets had risen to 600,000, clot was retractile, and the bleeding time normal. In fourteen days purpura and petechiæ had disappeared. The menstrual period decreased in duration from ten to three days. Later the platelet count dropped from 600,000 to 100,000, and irregular forms of platelets were again to be seen. However, clot retraction was normal and hemorrhage did not recur. In three months the anemia had disappeared. The patient was reported in excellent health and free from hemorrhage five years later.

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CASE II.—In 1917 Benecke reported a splenectomy on an unmarried woman, aged twenty-one years. Three years previously the patient had been under observation with anemia, epistaxis, and a pelvic condition which was probably due to hemorrhage although extra-uterine pregnancy had been suspected. At that time the hemoglobin was 35 per cent. Four months previous to the operation the patient was readmitted on account of severe anemia and prolonged menstruation. Apparently she had had petechiæ and purpura, together with epistaxis and prolonged menstruation, since the preceding examination. The hemoglobin was 30 per cent, the erythrocytes numbered 2,100,000, the leukocytes 3200 and the platelets 47,891. Medical measures failed to improve the anemia. Three months preceding the operation the hemoglobin was 30 per cent, and the platelets 38,370, and ten days preceding the operation the erythrocytes numbered 2,150,000, and the platelets 66,053. The spleen was not palpable.

Splenectomy was performed July 13, 1917. The spleen weighed 250 gm. and there was hyperplasia of the malpighian corpuscles. A smear from the spleen showed many platelets. On the third day after operation the erythrocytes numbered 3,250,000, the leukocytes 11,030, and the platelets 344,076. Two weeks after operation the hemoglobin was 42 per cent, the erythrocytes 3,580,000, the leukocytes 7400 and the platelets 664,000. A normal menstruation occurred. The patient was dismissed in a very satisfactory condition two months after operation; the hemoglobin was then 52 per cent, erythrocytes 4,176,000 leukocytes 4900, and platelets 577,800. Three months after operation the patient was apparently well.

CASE III.—Kaznelson's second case was reported in 1919. The patient was an unmarried woman, aged twenty-five years, who had suffered from purpura, epistaxis, and menorrhagia for five years, especially during the summer months. Preceding operation the platelet count was 500, the clot was non-retractile. During an acute exacerbation the erythrocytes fell very rapidly from 5,000,000 to less than 1,000,000. The spleen was barely palpable.

Splenectomy was performed November 18, 1916. Two hours afterward the platelet count had risen to 408,000 and the clot was retractile. The platelet curve decreased later to 20,000; however, the clot was still retractile, and slight epistaxis occurred but no serious bleeding either then or subsequently. Five months after the operation the platelet count was 33,000, and at one time had been as low as 10,000. There had been slight epistaxis at times, but no other bleeding. The menstruation lasted for three or four days, whereas formerly it had lasted ten days or more. Five years after splenectomy the patient had had no recurrence of hemorrhage and was apparently well.

CASE IV.—Kaznelson's third case was also reported in 1919. The patient was a girl, aged eleven years, who had had petechiæ, purpura, epistaxis, and hemorrhagic crises for three years. The platelet count was 6700; the clot non-retractile. The spleen was not palpable.

Splenectomy was performed December 18, 1916. Three days after splenectomy the platelet count was 267,000; in seven days it had dropped to 13,000 and moderate epistaxis and hematemesis occurred. The platelet count subsequently varied from 5000 to 28,000, and the patient continued to have a few petechiæ, but no ecchymosis, and epistaxis only rarely. Five years later the patient was also reported to be well without recurrence.

CASE V.—Minkowski, in 1919, reported a splenectomy performed on a man, aged fifty-three years. The patient had had petechiæ and purpura for several years, and epistaxis for two and a half years. Platelet counts varied from 14,000 to 29,000. The coagulation time varied from eight to fifteen minutes, the bleeding time was nineteen minutes; the tourniquet test was positive. Hemoglobin was 56 per cent, the erythrocytes numbered 5,200,000 and leukocytes 5400. The spleen was not palpable.

Splenectomy was performed October 7, 1919. The spleen, pathologically, was not large and showed no striking changes. Many platelets were present in smears. Seven hours after splenectomy the platelet count was 56,000; two days after splenectomy it was 100,000; and twenty-three days after it was 60,000. Twenty-one days after operation epistaxis occurred, and the bleeding time was found to be prolonged to fifteen minutes. One month after operation the platelet count was 25,000. Two months after operation there had been no further bleeding and the bleeding time was seven minutes.

CASE VI.—Ehrenberg, in 1920, reported a splenectomy on a girl, aged nineteen years, who formerly had had petechiæ for ten days preceding and during each menstruation. Menstruation was very profuse. Blood platelets were practically absent and the bleeding time was prolonged, especially preceding menstruation. It was usually between thirteen and twenty minutes, once it was ninety-seven minutes and once it was two hours. The coagulation time was usually normal. The spleen was not palpable.

Splenectomy was performed in 1918. Two and a half hours after splenectomy the platelet count had risen to 87,500. The following day it was 118,425, and five days afterward it was 684,700. The platelet count then gradually became reduced to 13,000 and later to 4000. The bleeding time varied from three minutes to six minutes; the anemia and purpura disappeared, and the menstruation became normal.

CASE VII.—Kaznelson, in 1921, reported a case of hemorrhagic purpura. The patient died at operation, apparently a "heart death." Details are not given.

CASE VIII.—Kaznelson reported his fifth case also in 1921, that of a woman, age not given, in whom splenectomy was successful. The platelets rose from 38,000 to 550,000. A protocol was not published.

CASE IX.—Minot, in 1921, reported a case in which splenectomy was performed in September, 1920, with favorable result. Details are not given. This patient was reported to be in good health two and a half years later. The platelet count before operation was 10,000, and after operation 300,000.

CASE X.—Retzlaff, in May, 1921, successfully performed a splenectomy for purpura hemorrhagica. Details are not given.

CASE XI.—Cori, in 1922, reported a splenectomy performed on a girl, aged thirteen years. She had had petechiæ, purpura and occasional epistaxis for four years, and once suffered prolonged bleeding after the extraction of a tooth. The father and the father's brother had had frequent epistaxis. The platelet count was extremely low, the bleeding time was six minutes, and the clot showed no retraction. The leukocytes numbered 8800, the erythrocytes 2,000,000. Normoblasts and myelocytes were present. The spleen was palpable.

Splenectomy was performed February 24, 1921. The spleen weighed 120 gm. Following the operation the platelet counts were 109,000 five hours after operation; 386,000 on the third day; 740,000 on the eighth day; 741,000 on the fifteenth day; 271,000 three months after operation; 280,000 four months after operation, and 145,000 eight months after operation. Five hours after operation the bleeding time was three minutes and the clot was retractile. Menstruation which had not occurred previously was established normally in seven months. Within ten months the platelet count had become reduced to 23,000, but bleeding had not recurred.

CASE XII.—Cori, in 1922, reported a second case. The patient was a woman, aged twenty-one years, who had suffered from profuse menorrhagia and had bled excessively after the extraction of a tooth. The platelet count before operation was very low. The spleen was palpable.

Splenectomy was performed November 27, 1921. The spleen weighed 320 gm., and contained many platelets. Eight hours after operation the platelet count was 63,750; the next day it was 307,000; on the fourth day it was 820,000; on the sixth day 862,000;

on the eighteenth day 1,150,000, and on the nineteenth day 89,500. Malarial parasites were found in the blood and the patient died from subphrenic abscess one month after splenectomy.

CASE XIII.—Steinbrinck, in 1922, reported the case of a girl, aged five years. At the age of two and a half years, she began to have crops of petechiæ and thrombopenia. Platelet counts ranged from 1300 to 18,000. Ten months later there was a recurrence. Two years later she had nose bleeds, and vomited blood. The spleen was not then palpable. Bleeding time was twelve minutes, and retraction of clot was incomplete after twelve hours. The platelet count was 700. As a result of continuous bleeding the hemoglobin was reduced to 15 per cent, and the erythrocytes to 1,770,000; the leukocytes numbered 12,100. The spleen was palpable at times.

Splenectomy was performed September 3, 1921. Bleeding ceased promptly. The platelets apparently did not increase, the count varying from 8000 to 18,000; many of the platelets were large and deformed. A splenic extract contained very few platelets. Nine weeks after operation the patient was in good general condition; there was no bleeding or petechial eruption. The tourniquet test however, was positive and the bleeding time was forty-one minutes. The leukocyte counts varied from 4330 to 26,400. Later the bleeding time was five and a half minutes and the clot showed feeble retraction after twenty-four hours. Five months after operation there was slight epistaxis and a few petechiæ, but the patient's general condition was good.

CASE XIV.—Bowen, in 1923, reported the case of a man, aged twenty-two years, who had had symptoms of purpura for eighteen years. Three months preceding operation there had been severe epistaxis, melena and bleeding from the gums. The hemoglobin was 18 per cent; erythrocytes numbered 1,648,000; the leukocytes 4800, of which 75 per cent were polymorphonuclears. The number of blood platelets was much decreased and the bleeding time varied from twenty minutes to two hours. The clot was non-retractile. Transfusions were given, and four days before operation the erythrocytes numbered 5,000,000, but the platelet count remained low, 2500. The spleen was palpable.

Splenectomy was performed August 28, 1922. Two hours after operation the platelet count was 17,000; within four hours it was 22,000; and the next day it was 190,000. The bleeding time was reduced to four minutes. Nine days after operation the platelet count was 608,000, and three weeks after operation it was 307,000. The patient was apparently in good condition. However, at the end of the fourth week he developed jaundice probably of the catarrhal type, and the platelet count became reduced to 100,000. One

month after operation the platelet count was 57,000, and the bleeding time was prolonged to fourteen minutes. In the ninth week the platelet count was 20,000, the bleeding time was seventy minutes, and slight epistaxis and purpura occurred. Twelve weeks after operation the jaundice began to clear; the platelet count was 50,000, the bleeding time twelve minutes. Four months after operation there had been no recurrence of bleeding; the platelet count was 95,000, and the bleeding-time eight minutes.

CASE XV.—Brill and Rosenthal in 1923, presented the first case in which splenectomy was performed, and which attracted general attention in this country. The patient, a girl, aged nineteen years, had had severe epistaxis at least once a year since the age of five. Purpura occurred and later prolonged menstruation. Eight transfusions had been given in the preceding eight years without permanent benefit. She was admitted to the Mt. Sinai Hospital, October 26, 1922, after three days of hematemesis and severe bleeding from the gums and nose. The hemoglobin was 38 per cent, the erythrocytes numbered 2,272,000, the leukocytes 6800, and the platelets 6400. The coagulation time was ten minutes (Lee); the bleeding-time ten plus minutes. The tourniquet test was positive. Clot retraction was absent. Direct transfusions of blood, and horse serum were given. The spleen was easily palpable.

Splenectomy was performed December 2, 1922. The spleen weighed 1400 gm. Microscopically it showed "myeloid metaplasia and hypertrophy of the malpighian bodies;" blood platelets were not seen. A fresh crop of petechiæ appeared and there was slight bleeding from the gums a few hours after operation, but later bleeding ceased. After operation the leukocytes increased to 56,000, later fluctuating between 8000 and 28,000. The platelets numbered 95,000 six hours after operation; one day later 225,000; and a week later 5000. The bleeding time was usually normal but occasionally prolonged. The tourniquet test was usually negative. Clot retractility was present the first month, absent the second month and present again the third month.

CASE XVI.—Brill and Rosenthal's second case was that of a boy, aged fifteen years. His illness began in April, 1919, with tonsillitis followed by petechiæ, bleeding from the gums, and painful joints with which he was confined to the hospital a month. Following this illness he had severe nose bleed in May, 1922, and occasional purpura on injury. Epistaxis recurred in July and November, 1922. He was admitted to the hospital November 22, 1922. A petechial eruption and bleeding from the gums were present. The patient was very anemic; the tourniquet test was at times positive, and at times negative; clot retraction was absent; the bleeding time was slightly prolonged, and at times normal. The leukocyte count was 10,000. The spleen was not palpable.

Splenectomy was performed December 30, 1922. The spleen was soft and slightly enlarged, weighing 300 gm. The malpighian bodies were visible. Oozing from the nose and wound stopped immediately after removal of the spleen, and the bleeding time was reduced to three minutes. Clot retraction was first present six weeks later. For a month following operation occasional crops of petechiæ and slight nose bleed occurred. One day after operation the platelet count was 31,200. The third day it fell to 1000, then gradually rose to 10,000 and 20,000. The bleeding time was slightly prolonged for a month.

CASE XVII.—Wild, in 1923, reported the case of a boy, aged fifteen years. A family history of bleeding had not been obtained. The patient had been subject to bleeding since early childhood, including bleeding from wounds, and extraction of a tooth had been followed by severe bleeding. At the age of eight, he had a hematoma at the knee, and anemia, at which time a diagnosis of hemophilia was made. On the morning of admission June 7, 1922, he experienced a sudden severe pain in the left side of the abdomen while straining at stool. He grew pale and was taken to the hospital. Ecchymoses but no petechiæ were found on various parts of the body. The hemoglobin was 36 per cent; the erythrocytes numbered 2,400,000. A diagnosis of rupture of the spleen was made, and a transfusion was given.

Splenectomy June 7, 1922 disclosed a rupture 5 cm. in length in a spleen which weighed 340 gm. The abdomen contained a large quantity of blood. Transfusion was necessary following operation. The day of the operation, the platelets numbered 92,500; the bleeding time was five minutes. On the following day the platelets numbered 81,000; the bleeding time was six and a half minutes. Five days after operation, the platelets numbered 324,000; on the thirteenth day 1,033,000; five weeks after operation 820,000; the bleeding time was two minutes. Nine months after operation the general health was excellent and there had been no recurrence of purpura. The coagulation time was persistently twenty minutes or longer, which is suggestive of a mild hemophilia.

CASE XVIII.—Hitzrot, in 1923, reported the case of a girl, aged eight years, who had had symptoms of purpura with epistaxis for three years. One month before operation there was an acute exacerbation accompanied by melena and hematemesis. The hemoglobin was 40 per cent, the erythrocytes numbered 2,400,000, the leukocytes 38,000 and platelets 40,500. The bleeding time was longer than twenty minutes, and the clot was non-retractile. The spleen was palpable.

Splenectomy was performed February 27, 1923. After the operation the platelet count rose to 600,000 and the bleeding time became

reduced to five minutes. Two months later the platelets were abundant and the bleeding time was two and a half minutes. Three months after operation there was continued general improvement and bleeding had not recurred.

The spleen in this case weighed 120 gm. (the patient's weight was only 47.5 pounds). On microscopic examination the lymphoid follicles showed large so-called germinal centers. Polymorphonuclear leukocytes and myelocytes were present in moderately large numbers, and the eosinophils were increased in number; collections of blood platelets were not seen.

CASE XIX.—Cohn and Lemann reported the case of a boy, aged five and a half years, who was first seen February 25, 1923. A history of familial bleeding was not obtained. Purpuric areas from 1 to 2.5 cm. had appeared recently. The tonsils had been removed several weeks previously. Slight anemia was present and the blood smears contained but few platelets. There was a recurrence of the purpura which did not subside after transfusion. The spleen was not palpable.

Splenectomy was performed June 3, 1923; the spleen was slightly enlarged. Shortly after operation there was a peculiar reaction, anaphylactic in type. This was thought to be due possibly to the expression of a toxic material from the spleen at operation. Following pneumonia recovery was satisfactory. Seven weeks after operation the platelet count was 145,000; four months after operation it was 200,000. Within six months the general condition was satisfactory and there had been no recurrence of purpura.

The remaining cases were observed at the Mayo Clinic. Eight of them have been reported in more detail elsewhere.

CASE XX.—A woman, aged thirty-one years, came under observation December 20, 1922. In October, 1921, petechiæ and ecchymoses had been noted and were more or less continuous afterward. In December, a tooth had been extracted with excessive bleeding. On October 1, 1922, severe epistaxis occurred and recurred, transfusions finally becoming necessary. November 3, uterine bleeding began and became excessive; transfusions again became necessary. There was no bleeding from bladder or gastrointestinal tract. Platelet counts were consistently below 100,000, and not infrequently below 50,000. The bleeding time was prolonged; the clot was non-retractile. During two months of personal observation, twelve transfusions were given. The hemoglobin dropped at one time to 18 per cent; the erythrocytes to 1,610,000. The spleen was palpable.

Splenectomy was performed March 7, 1923. The spleen was somewhat enlarged and weighed 210 gm. Six hours after operation the platelets numbered 202,000 and the bleeding-time was normal. The platelets numbered 727,000 on the eighth day and on the six-

teenth day 365,000. Slight uterine oozing occurred the third and fourth days, but did not recur. All evidence of purpura disappeared. Two years later the patient was still in good health.

CASE XXI.—A girl, aged twenty-three years, was admitted to the clinic June 12, 1923 on account of excessive menstruation. She had had ecchymoses on slight injury for thirteen years. Five years previously menstruation became very excessive and she was confined to bed for five months. Nose bleeds had been frequent between the ages of fifteen and nineteen. At the time of admission she was moderately anemic; the platelets varying from 28,000 to 100,000, the bleeding time was prolonged. Transfusions were given with temporary benefit, but excessive menstruation and other manifestations of purpura continued. The spleen was palpable.

Splenectomy was performed October 29, 1923. The spleen weighed 200 gm. The following day the platelets numbered 146,000, on the sixth day 638,000. All signs of purpura promptly disappeared and menstruation became normal. One year later after a severe reaction following vaccination a crop of petechiæ appeared but faded in a few days. The menstruation did not become excessive. Seventeen months after operation the patient is apparently well.

CASE XXII.—A man, aged twenty-four years, was first seen January 9, 1920. For twelve years he had had severe nose bleeds. Slight oozing from the gums was almost continuous, and petechiæ appeared frequently. Moderately severe anemia was present chiefly as a result of epistaxis. One Wassermann test was positive but an investigation for syphilis was negative. Improvement followed transfusion. The patient returned at intervals; he did not have severe hemorrhages, but he could not exert himself because of the development of petechiæ, ecchymoses and bleeding from the gums. Usually the platelets were under 100,000. The tourniquet test was positive; the clot was non-retractile. Bleeding time was occasionally prolonged. The spleen was not palpable.

Splenectomy was performed February 22, 1924. The spleen weighed 220 gm. Bleeding from the gums ceased immediately. Slight nose bleed recurred on the fifth day, but after that time all manifestations of purpura disappeared. Two weeks after operation the platelets numbered 260,000; the bleeding time was two minutes. Thirteen months after operation the patient apparently is well.

CASE XXIII.—A girl, aged eleven years, was admitted March 11, 1924, because of epistaxis, petechiæ and ecchymoses, which had been recurrent for five and a half years. Three years previously she had been confined to the hospital seven weeks and was transfused. The patient was moderately anemic; the platelets numbered

less than 50,000; the bleeding time varied from thirty-eight minutes to one hour. A tourniquet test was positive. The spleen was easily palpable.

Splenectomy was performed March 18, 1924. The spleen weighed 168 gm. (the child weighed 92 pounds). By the fifth day the platelet count had risen to 430,000, and the bleeding time had become reduced to two and a half minutes. The patient had nose bleed the second day after operation. From four to six weeks after operation the patient suffered from a severe cold, and had slight nose bleed and a few petechiæ. One year following splenectomy there has been no recurrence of purpuric manifestations and the patient is in excellent health.

CASE XXIV.—A man, aged thirty-two years, came under observation August 28, 1924. Two years previously he began to have purpuric areas on the slightest injury which would spread widely before beginning to clear up. Petechiæ occurred and scratches would bleed excessively. He had bleeding from scratches on the scalp, bleeding into the sclerotics, and bleeding from nose and gums. Blood was passed in the urine and stools. At times purpuric areas would leave nodules under the skin, and a mild degree of arthritic pain was complained of. The platelet count was 36,000, the bleeding time was fifteen minutes; the tourniquet test was positive; and the clot was non-retractile in two hours. The spleen was barely palpable.

Splenectomy was performed October 8, 1924. The spleen weighed 164 gm. On the sixth day the platelets numbered 684,000, and the bleeding time was five minutes. On the eleventh day the platelets numbered 816,000; the bleeding time was two and a half minutes. The massive purpuric areas and other manifestations of purpura never recurred, and the arthritic pains disappeared. The patient continues to be in good health five months after operation.

CASE XXV.—A girl, aged eleven years, was admitted September 22, 1924. Petechiæ had appeared suddenly five and a half years before, since which time petechiæ had recurred with ecchymoses and epistaxis. The gums bled easily, and there had been occasional bleeding into the sclerotics. Bleeding from the vagina once followed a fall, and bleeding from the bowel had been noted. At the time of admission the slightest exertion brought on bleeding and at times attacks of fever to 101° F. Marked anemia was present. The platelets numbered 54,000; the bleeding time was ten minutes; the tourniquet test was positive; and retractility of the clot did not occur in three hours. On two occasions the platelets rose temporarily to 180,000. The spleen was easily palpable and firm.

Splenectomy was performed October 10, 1924. The spleen weighed 202 gm. and was definitely enlarged in comparison with the

weight of the patient. On the third day the platelets numbered 643,000, and the bleeding time was three and a half minutes. The highest platelet count was 780,000 on the sixth day. Eighteen days after operation the platelet count became reduced to 88,000 but the bleeding time was two and a half minutes. No fresh hemorrhages occurred. Five months after operation the patient continued in good health.

CASE XXVI.—A girl, aged fifteen years, was examined September 24, 1924. Petechiæ and purpura had been present for ten years. Epistaxis had occasionally occurred. Bleeding from the gums had never been troublesome. Menstruation began at thirteen, occurred at intervals of from four to six weeks, and lasted from four to thirty days. At the onset of menstruation she had been confined to the hospital for five weeks and was given several transfusions. At the time of admission the hemoglobin was 14 per cent, the erythrocytes numbered 1,370,000, and the platelets 42,000. The bleeding time was six minutes; clot retractility was absent in twenty-four hours. Following one transfusion improvement was very rapid. The platelets varied from 42,000 to 166,000, but most of the time were in the neighborhood of 100,000. The spleen was palpable and firm.

Splenectomy was performed October 16, 1924. The spleen weighed only 125 gm. but at the time of operation was estimated as twice normal size. No bleeding occurred after operation. The platelets on the third day numbered only 64,000, on the fifth day 516,000, but the bleeding time was prolonged, seven and a half minutes, and retractility of clot did not occur in six hours. Even on dismissal, the fifteenth day, the bleeding time was six and a half minutes. Clot retraction was not satisfactory in twenty-four hours, although the platelets numbered 408,000. Symptoms had not recurred five months later.

CASE XXVII.—A girl, aged eighteen years, was admitted January 30, 1920. Menstruation had begun five years previously with profuse bleeding, necessitating absolute rest for four weeks and uterine packs. More or less frequent periods of disability occurred because of uterine hemorrhages. Nose bleeds had occurred since childhood, ecchymoses and petechiæ had been present for at least five years, and bleeding from the gums had been continuous for a year. The hemoglobin was 15 per cent; the erythrocytes numbered 1,800,000. After a series of four transfusions the blood was normal.

Curettage was performed April 24, after which no serious difficulty with uterine hemorrhage was experienced. The patient was under observation for four years and was at all times partially disabled by petechiæ, ecchymoses, bleeding from the gums, and occasionally profuse menstruation. The platelets varied from 42,000 to 72,000 with occasional elevations above 100,000, and once

it was 206,000. The bleeding time was prolonged; the tourniquet test was positive; the clot was non-retractile. The spleen was not palpable.

Splenectomy was performed October 23, 1924. The spleen weighed, after loss of its blood, only 92 gm. Four hours after operation the platelets numbered 200,000; on the ninth day 840,000. On the fifth day there was slight retraction of the clot in thirty minutes. All hemorrhagic manifestations ceased. Five months later the patient was in excellent health.

The following case has not been previously reported, and the data will therefore be given more in detail. It constitutes the ninth case of our series.

CASE XXVIII.—A man, aged twenty-seven years, came under observation February 19, 1924. There was no history of hemophilia, purpura, or epistaxis in the family. He had had severe recurrent hemorrhages from the nose for a period of eight months. For six months large and small purpuric areas had appeared on the body, especially on the arms and legs. Bleeding from the gums had occurred at times, and on several occasions hemorrhages into the conjunctiva.

Petechiæ were present. The hemoglobin was 73 per cent, the erythrocytes numbered 4,480,000, and leukocytes 13,200; the differential count was not abnormal. The platelets varied from 52,000 to 134,000; the bleeding time was from three to twenty minutes; the coagulation time by the Boggs method varied from four and a half to nine minutes, and by the Lee method it was twelve minutes; the calcium time was twelve minutes; the prothrombin time was not definitely prolonged. A tourniquet test was positive. The clot did not retract satisfactorily in twenty-four hours. Large septic tonsils, an area of periapical infection and a traumatic ulcer on the septum were noted. Three injections of 20 cc of whole blood subcutaneously were given. These were followed by extraction of one tooth March 6, and by tonsillectomy March 11. Following tonsillectomy, oozing continued at intervals for six days and the patient became pale. The erythrocytes dropped to 2,990,000, and the hemoglobin was 45 per cent. Two transfusions were then given; bleeding ceased after the first one.

The patient was dismissed March 28, 1924, and returned September 24. There had been no serious hemorrhage since the former dismissal, although bleeding from the gums and purpuric areas recurred. The blood platelets were 102,000, coagulation time by the Boggs method was five and a half minutes and bleeding time three minutes; coagulation time by the Lee method was thirteen minutes, calcium time was twelve minutes, and the prothrombin time was slightly prolonged. The tourniquet test was not definitely positive.

The patient was dismissed September 25, 1924, and returned January 12, 1925. Epistaxis had occurred three times, and there was bleeding from the gums on the slightest trauma. The tourniquet test was positive. The blood count was normal, the platelets numbered 50,000, the coagulation time by the Boggs method eight and a half minutes, bleeding time four minutes, coagulation time by the Lee method nine and a half minutes, and calcium time fifteen minutes. The prothrombin time was definitely prolonged. Clot retraction was absent at two hours and very slight at four hours. The erythrocytes showed normal fragility. The spleen had not been palpable at any time while this patient was under observation.

Splenectomy was performed January 12. The spleen was described as being slightly larger than normal, but it weighed only 140 gm. The patient's convalescence was satisfactory. On the eighth day after operation the blood platelets numbered 360,000; on the thirteenth day they had risen to 504,000. The bleeding time was normal after operation. On the eleventh day the coagulation time by the Lee method was six minutes, the calcium time was eight and a half minutes. Three weeks after operation the hemoglobin was 67 per cent, erythrocytes numbered 3,840,000, and the leukocytes 10,600. The differential count showed nothing of special importance. The platelets numbered 308,000; the coagulation time by the Boggs method was six minutes, by the Lee method nine minutes, the bleeding time was two minutes, the calcium time ten and a half minutes, and prothrombin time normal. Retractility of the clot was slight in one hour, marked in two hours, and apparently complete in five hours. The tourniquet test was negative. Three months after operation the patient was well.

Summary. *The Clinical History.* Most of the histories in the collected series of cases exemplify the chronic recurrent type of purpura hemorrhagica with low platelet count, non-retractile clot, long bleeding time, and positive tourniquet or capillary resistance test. In many cases petechiæ and ecchymoses dated from childhood. Bleeding in most cases was from the nose, gums, and uterus. Bleeding from the bowel occurred in 4 cases and from the bladder in 1. In 3 blood was vomited. Extraction of teeth and tonsillectomy were quite frequently followed by troublesome oozing even after preliminary preparation. Bleeding into the sclerotics was noted in 2 cases. The patient in Case I during a remission had given birth to a child without serious incident; in Case II, in which extra-uterine pregnancy had been suspected, the pelvic condition was probably due to hemorrhage. In Case XXIV purpuric areas became quite extensive before beginning to clear up, and some of these developed into subcutaneous hematomas leaving nodules which disappeared very slowly; troublesome bleeding occurred from scratches.

In Case XI the patient's father and father's brother had had frequent epistaxis, but the patient did not have hemophilia. In Case XVIII the purpura had existed since infancy and a hematoma occurred at the knee when the boy was eight. He was admitted with a rupture of the spleen following straining at stool. Splenectomy was performed with a subsequent disappearance of all hemorrhagic manifestations. The platelets were said to be few in number on inspection of the smears before operation, but the coagulation features had some of the characteristics of hemophilia. The author, however, believed that hemophilia had been excluded. In Case XXVII curettage was effective in arresting severe metrorrhagia; the menstruation was somewhat profuse but not excessively so afterward up to the time of splenectomy four and a half years later. This observation may be important in the control of uterine hemorrhage which frequently persists in spite of packing and the use of coagulants and transfusions; the result of curettage is usually feared in such cases, possibly unnecessarily in view of the fact that in cases of purpura hemorrhagica gross wounds do not cause uncontrollable bleeding. Patients are known to have had major operations in the course of the disease aside from removal of the spleen.

The use of coagulants was ineffectual or only temporarily effectual. Subcutaneous injection of whole blood seemed to be more effective than coagulants. Radium exposures over the spleen were also temporarily effective. In the Mayo Clinic series, transfusions by the citrate method were efficacious in improving the patient's general condition and the blood, and in most instances in decreasing the amount of bleeding and preparing them for splenectomy. Absolute rest in bed and quietness in bed are essentials in the medical care.

In Cases XVI and XXIV arthritic pain was a prominent complaint but actual arthritis and hemorrhage into the joint were not demonstrated. This symptom disappeared promptly after splenectomy.

In Case XXII a Wassermann reaction was positive but a thorough investigation for syphilis was negative. It is no longer surprising to obtain a false positive Wassermann reaction in any serious blood dyscrasia.

The duration of the symptoms was from six months to eighteen years. In 21 cases it was longer than three years; the duration was not given in 3 cases. No case of acute fulminating hemorrhagic purpura has been reported in which splenectomy was attempted. Of the 28 patients only 8 are known to be males; in 3 cases the sex was not given. The youngest patient was three years, the oldest fifty-three. All the others were younger than thirty-six, and 18 were younger than twenty-five years; the ages of 4 were not recorded. The disease is predominantly one of youth and adolescence.

The Spleen. In 4 of the 28 cases the size of the spleen is not mentioned, while in 15 of the remaining 24 it was palpable; in 9 it was not palpable. Usually it appeared to be only slightly enlarged. It is quite evident that palpability or even enlargement of the spleen is not essential to the decision for splenectomy. In 15 cases the weight of the spleen is given; in 1 it was 1400 gm.; in the remaining 14 cases it averaged 204 gm. In 1 case, that of an adult aged twenty-two years, it weighed only 92 gm. The spleen in children was slightly larger in proportion to their weight than the spleen in adults. In our cases the weight of the spleen was less than would have been expected in the consideration of its apparent size on physical examination, probably indicating that the organ in purpura hemorrhagica contains a large quantity of blood. The pressure exerted at the time of operation would be expected to reduce considerably the size of a vascular organ.

The Operation and Mortality. No difficulty with excessive bleeding has been encountered immediately following operation. The excessive oozing at operation disappears promptly after the spleen is removed. Transfusions have been necessary in a few of the cases, before, during, or after operation chiefly as a supportive measure. Two operative deaths occurred, 1 reported as a "heart death" at the time of operation, the other following subphrenic abscess. In the other cases convalescence has been very rapid and satisfactory.

Postoperative Bleeding. In 6 of the 26 cases slight epistaxis occurred chiefly during the first few days after operation. In Case III slight epistaxis occurred at times for five months following operation, the platelets were still low, but no other form of bleeding appeared and the patient was reported as well five years later. In Case V slight epistaxis occurred twenty-one days after operation. In Case XIII petechiæ appeared five months after operation, but were transient. In Case XIV epistaxis accompanied catarrhal jaundice one to three months after operation. In Case XVI occasional crops of petechiæ appeared for a month following operation. In Case XXIII petechiæ accompanied an acute respiratory infection one month after operation. Petechiæ appeared after convalescence in 2 cases. In Case XXI they appeared one year after operation after three days' severe reaction following vaccination, and cleared up promptly. In all cases, so far as can be ascertained, these slight evidences of the hemorrhagic tendency were transient. Their appearance suggest the possibility that foci of infection might still be present in these cases. The logical procedure in cases of purpura hemorrhagica would seem to be splenectomy followed by elimination of all possible foci; the latter portion of the treatment cannot be safely neglected.

The Platelets. In most of the cases before operation, at some time in the course of each case, the platelets numbered less than 50,000. The platelet level before operation in cases in which multi-

ple counts are recorded was below 100,000, except for occasional short periods, usually days, in which the platelets might rise approximately to normal. In Case V at one time no platelets were found. In a few instances the counts were in the hundreds.

After operation the platelets almost always rose rapidly to above normal, and in three instances more than 1,000,000 are recorded. In two instances they remained below 50,000 but even in these cases the ultimate results were satisfactory. In 6 cases after a rise in the platelet count, a subsequent fall below 50,000 is noted. Active bleeding did not recur, although petechiæ and epistaxis were sometimes present when the platelets became reduced. However, transient petechiæ and epistaxis occurred also in some of the cases in which the platelets were not reduced. These facts indicate that the increased number of the platelets is only one factor in the arrest of purpuric manifestations. It is well known that the platelets are morphologically abnormal in this disease, and more or less complete recovery from this would be likely to influence the clinical result. A study of the morphology of platelets by means of the ultramicroscope may be expected to add to the information on this subject.

In 8 cases the platelet counts were made from two to eight hours after splenectomy; they varied from 17,000 to 202,000, while in 7 cases they were over 50,000 and in 3 over 100,000. This rapid rise of the platelets within a few hours of splenectomy is almost as striking as the cessation of bleeding. In almost all instances the platelet counts made one day after operation were more than 100,000. The highest counts are usually recorded between the sixth and the ninth days, although in four instances they were recorded on the second and third days, and in one instance as late as the twenty-first day. In Case XVI the count did not rise above 31,200 during convalescence.

More platelet counts over a long period of time are necessary after splenectomy to determine the postoperative platelet level. The data at hand indicate that frequent counts before operation show a platelet level below 100,000 with occasional elevations above this even up to normal, and following operation the maintenance of a higher level with occasional depression below 100,000 except in the occasional case in which the platelet level may remain low for longer periods of time.

The Tourniquet Test. This test was always positive when applied during active periods of purpura and not infrequently during remissions. After operation it became negative soon after the petechiæ and ecchymoses faded.

The Bleeding time and Retractility of Clot. Two and a half minutes or less may be regarded as a normal bleeding time. In many of the cases the bleeding time was longer than eight minutes and occasionally longer than one hour, although not infrequently it was approximately five or six minutes. After splenectomy there

was great variability in the promptness with which the bleeding time became reduced. In 3 cases it is reported as normal within a few hours. In most of the cases it became reduced quite promptly

FINDINGS IN REPORTED CASES OF THROMBOCYTOPENIC PURPURA HEMORRHAGICA.

Case.	Author.	Date of operation.	Sex.	Age, yrs.	Duration before operation, yrs.	Platelets.		Weight of spleen, mg.	Last report after operation, mos.	Remarks.
						Before operation.	After operation.			
I	Kaznelson	1916	F.	36	10	600	500,000	..	60	No recurrence; well.
II	Kaznelson	1916	F.	25	5	700	408,000	250	60	Slight epistaxis; well.
III	Kaznelson ¹	1915	F.	11	3	6700	267,000 13,000	..	60	Slight epistaxis for 5 mos.; well.
IV	Benecke	1917	F.	20	3+	38,370	1,783,514	..	3	No recurrence.
V	Ehrenberg	1918	F.	19	Several	None found	684,700 13,000	No recurrence.
VI	Minkowski	1919	M.	53	2½	14,000	100,000	..	2	Slight epistaxis 21 days after opera.; good result.
VII	Minot	1920	10	10,000	300,000	..	24	No recurrence.
VIII	Kaznelson	1921	"Heart death" at operation.
IX	Kaznelson	1921	F.	38,000	550,000	..	Recent	No recurrence.
X	Retzlaff	1921	Details	not given	No recurrence.
XI	Cori	1921	F.	15	4	2200	743,000 23,000	..	10	No recurrence.
XII	Cori	1921	F.	21	Several	Very low	1,150,000	320	1	No recurrence; death; subphrenic abs.
XIII	Steinbrinck	1921	F.	3	1	700	10,000 40,000	..	6	Petechiæ 5 mos. after operation; good result.
XIV	Bowen	1922	M.	22	18	2500	17,000 608,000	..	4	Catar. jaundice with epistaxis 1 to 3 mos.; good result.
XV	Brill and Rosenthal	1922	F.	19	14	6800	290,000 10,000	1400	4	No recurrence.
XVI	Brill and Rosenthal	1922	M.	15	3½	400	31,200	300	4	Petechiæ for 1 mo. good result.
XVII	Hitzrot	1923	F.	8	3	24,000 4000	10,000 50,000 600,000	120	3	No recurrence.
XVIII	Wild	1922	M.	15	Several	Not given	92,500 1,033,000	340	9	Emergency; a spontaneous rupture of the spleen; no recurrence.
XIX	Cohn and Lemann	1923	M.	5	½	Few	200,000	..	6	Chiefly purpura before opera. no recurrence after opera.
XX	Mayo Clinic	1923	F.	31	1½	24,000	727,000	210	19	No recurrence.
XXI	Mayo Clinic	1923	F.	23	13	54,000	638,000	200	12	No recurrence.
XXII	Mayo Clinic	1924	M.	24	12	72,000	280,000	220	8	No recurrence.
XXIII	Mayo Clinic	1924	F.	11	5	46,000	430,000 50,000	168	7	Sl. recurrence with cold 6 wks. after op., none since.
XXIV	Mayo Clinic	1924	M.	32	2	36,000	816,000	164	5	No recurrence.
XXV	Mayo Clinic	1924	F.	11	5	54,000	780,000 88,000	202	5	No recurrence.
XXVI	Mayo Clinic	1924	F.	15	10	42,000	516,000	125	5	No recurrence.
XXVII	Mayo Clinic	1924	F.	18	15+	42,000	840,000	92	5	No recurrence.
XXVIII	Mayo Clinic ²	1925	M.	27	1	52,000	504,000	140	3	No recurrence.

¹ Schmidt reported 2 cases which seem to be identical with those reported by Kaznelson.

² New case.

to less than eight minutes, and in from five to eighteen days to less than three minutes. In Case XIII the bleeding time, however, was forty-one minutes nine weeks after operation. Still greater variability is shown in the retractility of the clot. In 2 cases retractility was satisfactory within a few hours of operation, in another it was absent in fifteen days. In Case XV clot retraction was present the first month, absent the second, and present the third month. Apparently the recovery of this function is likely to be delayed longer than that of the other factors of coagulation. However, the test for retractility has not yet been standardized, and some of the unsatisfactory results may be due to this fact.

The Pathologic Condition of Extirpated Spleens. A detailed description of the condition of spleens removed at operation cannot be undertaken in this paper. In general, it has been noted that spleens removed in the Mayo Clinic cases are vascular, and usually soft, and show nothing of outstanding importance either grossly or microscopically except the presence of an abnormally large number of neutrophilic polymorphonuclear leukocytes. It would seem appropriate to say that the splenomegaly of this disease is an acute splenitis.

Conclusions. The recurrence of petechiæ in some of the cases, the slowness with which the bleeding time becomes reduced, and the variability in connection with the recovery of the retractility of the clot, indicate that although a change has been brought about by splenectomy sufficient to arrest gross hemorrhage, the finer mechanism of coagulation requires a complex readjustment on the part of the organism, which may or may not become complete and permanent. A few of the patients have remained somewhat anemic. However, the uniformly good results indicate at least a temporary cure.

So far as is known at present, only well defined cases of purpura hemorrhagica should be recommended for splenectomy. A correct diagnosis, therefore, becomes especially important. Aplastic anemia with hemorrhagic features may be most difficult to differentiate from hemorrhagic purpura. A persistent and extreme leukopenia and a low reticulated cell count are a characteristic of aplastic anemia, and the period of bleeding has been preceded by a period of rapidly developing anemia. Borderline conditions also occur with confusing coagulation features in which a decision between hemophilia and hemorrhagic purpura is impossible.

More frequent estimations of the platelets and the various features of coagulation both preceding and following splenectomy, standardization of the test for the retractility of the clot, and an understanding of the morphologic and chemical abnormality of the platelet and the function of the spleen in relationship to the destruction of platelets, are especially important matters for immediate study.

Since the preparation of this paper 6 other cases have been reported in the literature, 2 by Ricaldoni and Albo, 2 by Sutherland and Williamson, 1 by Bass and Cohn, and 1 by Flexner. These are typical cases, and in general the results of splenectomy correspond to those observed elsewhere. Another borderline case, with some signs of an acute myelosis, has been reported by Mitchell and Farley. The fatal outcome a few weeks after splenectomy was preceded by considerable symptomatic improvement, and a partial high intestinal obstruction must at least be considered a factor in the unfavorable result.

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A CLINICAL STUDY OF QUINIDIN THERAPY.

REPORT OF FIFTY-TWO CASES OF AURICULAR FIBRILLATION WITH RESTORATION OF THE NORMAL RHYTHM IN SEVENTY-NINE PER CENT.

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THE introduction of quinin as a therapeutic agent in the treatment of certain phases of heart disease by Wenckebach ten years ago, and its more practical application as quinidin by Frey in 1917, has led to many and varied estimations of its value, considerable experimentation to account for its action, particularly by Lewis, and divergent results from its clinical application. Hitherto quinidin has perhaps yielded far more brilliant results in the experimental study of the nature of auricular fibrillation than in the treatment of that condition, but there seems reason to believe that this is true only because our technic of the use of quinidin as a therapeutic agent is still far from being perfected and standardized. For this reason an analysis of the results, being obtained by means of a standard method of treatment of an unselected group of cases, should be of distinct value.

The general opinion concerning the use of quinidin in auricular fibrillation seems to be that under favorable conditions the fibrillation is converted to a sinus rhythm in about 50 per cent of the cases, notably those with a recent onset. Furthermore, it has been generally reported that the duration of the regular rhythm frequently has been short, such as to confer no real benefit to the patient, who perhaps may assume the risk of a fatal termination of his disease by the accident of embolic phenomena or of respiratory paralysis. The experience obtained during the treatment of the 52 cases which compose this study has not been such as to confirm this general impression, but rather leads to a more optimistic attitude toward the use of quinidin in auricular fibrillation.

The object of this paper is to describe in detail the method of treatment of auricular fibrillation with quinidin, which is being used in the First Medical Division of the New York Hospital, and to discuss the results obtained.

While as a whole these results are not remarkable, because of the several failures which occurred during our earlier experience with quinidin therapy, those more recently obtained seem to be sufficiently successful to justify their publication. The plan of treatment now in use is the result of experience obtained during the past three

years with quinidin in 52 cases of chronic heart disease complicated by the presence, over a considerable period, of auricular fibrillation.

The more important theoretical considerations involved in the use of quinidin must be thoroughly appreciated in order to understand the rationale of the therapy. Lewis¹ has shown that in the fibrillating heart, under the influence of quinidin, the rate of the auricular oscillations is slowed, and the ventricular rate increased, until in certain cases the lengthening of the refractory period over the conduction time abolishes the circus movement and the pace-maker resumes its function.

It has been noticed that quite often during quinidin administration the ventricular rate reaches such a height that the drug must be withdrawn before definite therapeutic effects have been obtained. As a means of preventing this, advantage is taken of the action of digitalis in fibrillation, since it effects a block at the auriculoventricular junction and prevents the weaker impulses arising in ectopic foci in the auricle from causing ventricular contraction. By the use of digitalis in large doses the acceleration of the ventricular rate which sometimes occurs during quinidin treatment may be counteracted, and one of its most unpleasant effects avoided. It has been suggested that the action of quinidin may be impeded^{2, 3} by the simultaneous use of digitalis because it is known that the latter drug sometimes increases the rate of fibrillation in the auricle. However, Lewis⁴ maintains that "The slight disadvantage to the quinidin reaction which follows from simultaneous digitalis therapy is often more than counterbalanced by the control of the ventricular rate which is obtained." The latter view is certainly substantiated by the results in the present series of cases, although occasionally quinidin alone will effect a reversion of the rhythm. Conditions which tend to accelerate the heart rate, such as exercise or mental excitement or fever, must be avoided during the administration of quinidin because they tend to relieve the delayed conduction time established by digitalis and thus defeat its purpose in that respect.

The plan of treatment consists in the preliminary thorough digitalization of the patient, complete rest in bed and other measures if necessary, to bring his heart to the best possible degree of compensation. The common criteria are used to estimate the condition of the circulation, such as the slowing of the apex rate, a decrease in the pulse deficit, loss of edema and congestion as far as possible, and an increase in the vital capacity. The heart rate should be reduced to 60 to 80 beats per minute, and should not fluctuate materially during any twenty-four-hour period. To facilitate the action of digitalis all exercise should be prohibited, mental excitement guarded against, and finally the presence of fever avoided if possible, before beginning the administration of quinidin. It has been noted in the study of these cases that the quinidin treatment of fibrillation was seldom successful when the patient was permitted

to be out of bed, or when the drug was administered during a febrile period, concomitant with a rise in the pulse rate; the need for avoidance of these factors cannot be too strongly emphasized. It is the careful attention to the details of treatment which may bring success in cases somewhat resistant to the effects of the drug.

When the general condition of the patient has been improved as much as possible by means of rest and digitalis therapy the use of this drug is discontinued temporarily, and the administration of quinidin begun within twenty-four hours. The method of administering quinidin itself is of such importance that it deserves special emphasis. Quinidin sulphate is given in capsules in 0.4 gm. doses every four hours day and night. Lewis^b has made a study of the changes in the auricular and ventricular rates produced by a single dose of quinidin, and has found that the heart recovers from the effect of the drug in such a short time that it must be given at frequent intervals. According to this investigator, a depression of the auricular oscillations must be maintained at a rate of 250 to 300 per minute in order to secure a reversal of the rhythm. If the drug is not given at night the effect of the previous day's administration will have been lost by the following morning. The necessity of administering the drug continuously throughout the night as well as the day is apparent and, indeed, failure at times to restore the fibrillating heart to the normal rhythm may be ascribed to this omission. If the normal sinus rhythm is attained without the appearance of untoward symptoms quinidin is withdrawn within twenty-four hours and digitalis given in maintenance doses, usually about 30 minims of the tincture per day, if necessary.

In 2 recent cases (Nos. 193 and 359) the usual dosage of quinidin had no effect on the rate or rhythm of the heart and did not cause symptoms of cinchonism. The dosage was then doubled, 0.8 gm. being given every four hours, and after a few doses the heart rate became regular in each case. It seems therefore that all cases do not react to the same concentration of the drug in the body, and that the reaction of the patient alone should be the final guide as to the amount of quinidin which may be given in a single dose.

All the cases upon which this study is based have been chronic auricular fibrillation, and in by far the greater number there has been the definite valvular damage of rheumatic endocarditis. In 52 consecutive cases treated with quinidin on this service there were 41, or about 79 per cent, in which the normal sinus mechanism was restored. Of these 41 cases it is known that in 6 the heart had remained regular for more than a year, and in 12 for more than six months. Six additional cases have maintained a sinus rhythm for more than three months. Many of the cases are still under observation and many of the remaining (beside the 24 here accounted for) we have been unable to follow. In 11 cases quinidin as given did not restore the sinus rhythm. Several of

these were treated under unfavorable circumstances, and before the method had become standardized.

Failure to respond to treatment may be determined in a large percentage of the cases from a study of their records. The causes of failure fall into two general groups: (1) Faulty administration of either digitalis or quinidin or both, and (2) improper management of the cases with reference to exercise or mental excitement or the presence of fever. In the first group there are cases in which digitalis was either not employed at all or given in insufficient amount to produce the desired effect, and several times the rapid ventricular rate resulting from a few doses of quinidin made the patient so uncomfortable (because of the rapid rate) that the drug had to be withdrawn before the normal sinus rhythm could have been established. This applies particularly to the early cases. In many successfully treated cases a moderate ventricular acceleration occurred, lasting for several hours after the discontinuance of the drug, while in others the rate was depressed. In 1 case the rate upon resumption of the normal rhythm was 50 beats per minute. This resulted after 4.8 gm. of quinidin had been given during twenty-four hours. In 1 unsuccessful case (No. 194) quinidin had no effect on the rate, nor did it cause symptoms of cinchonism, and it is probable that not enough of the drug was given in each dose. In the second group of unsuccessfully treated cases several patients were out of bed, and several had a slight fever at the time of the administration of quinidin. These factors tend both to destroy the blocking effect of digitalis on the ventricular rate, and to hinder the improvement of the general circulation. A study of the case records shows that an essential point was to keep the patient at absolute rest in bed. With few exceptions, in all the cases in which the quinidin treatment was successful the rules outlined above were carefully adhered to, and with similar exceptions all the cases which failed to respond to the drug showed by their charts that the above conditions were not followed. There were 3 cases in which no specific reason could be assigned for the failure of quinidin to restore the rhythm. Separate consideration must be accorded 2 cases in which the fibrillation was converted to a flutter under the influence of quinidin (Nos. 330 and 356). These 2 reverted to fibrillation under the influence of digitalis and are classed as unsuccessfully treated cases.

In thyrotoxicosis complicated by cardiac decompensation and auricular fibrillation quinidin treatment is definitely indicated. In this series there are 7 such cases and in all the sinus rhythm was restored. In 3 of the cases the return to normal rhythm was transitory, but in the remaining 4 a regular mechanism has been maintained for periods of six, five, four and two months respectively. From this small series general conclusions cannot be safely drawn with regard to their management. It may be, however, that in

the preoperative preparation of this type of patient a regular heart rhythm improves the surgical prognosis, and in our experience can be easily attained.

In the study of the electrocardiograms of the successfully treated cases it was noted that the *P-R* interval was prolonged in all those in which the sinus rhythm persisted for any considerable period of time. At the time of the resumption of the normal rhythm the *P-R* intervals varied between 0.18 and 0.34 second. These cases divide themselves into two groups: One in which it seemed that

Case No.	Date of admission.	Degree of decompensation.	Duration of fibrillation, months.	Amount digitalis before quinidin, drams.	Amount quinidin before revision, grams.	Pulse rates.		<i>P-R</i> intervals second.	Duration of restored rhythm, months.	Remarks.
						Before quinidin.	After restored rhythm.			
296	8/22	Marked	4	5	0.4	80	200	0.24	26	
139	3/22	Moderate	18	5	2.4	68	68	0.28	28	
308	1/23	Marked	12	8½	2.4	64	88	0.32	18	
168	7/23	Marked	18	12	4.2	64	64	0.22	12	
280	1/22	Marked	24	1	0.8	66	118	0.20	12	
325	7/23	Marked	24	7	1.6	72	80	0.30	10	
270	7/21	Moderate	12	2	6.0	64	70	0.20	6	
176	1/22	Marked	24	2	14.4	88	100	0.24	6	
202	2/24	Moderate	2	8	2.0	76	76	0.20	6	
195	7/24	Moderate	7	8	0.8	80	102	0.24	4	
124	11/21	Marked	12	3	3.0	92	80	0.21	6	
130	3/22	Marked	4	2½	3.0	80	88	0.21	6	
169	2/23	Slight	3	9	5.0	76	92	?	3	
288	3/22	Marked	3	11	1.6	78	80	0.18	12	
129	3/22	Slight	1	2½	3.2	68	68	0.18	1	
146	7/22	Slight	3	4	0.4	88	88	0.20	1	
349	1/24	Moderate	3	5	5.0	96	96	0.32	6	
345	12/23	Slight	1	6	3.6	88	88	0.24	3	
337	10/23	Moderate	4	7½	0.8	72	72	0.20	6	
351	2/24	Moderate	12	9	3.2	72	72	0.22	3	
95	8/23	Slight	?	5	2.8	96	96	0.20	3	
10	11/22	Moderate	6	5	1.6	100	100	0.18	6	Thyrototoxicosis.
11	10/22	Marked	6	25	2.0	96	96	0.16	2 days	Thyrototoxicosis.
17	1/22	Slight	?	3	3.2	98	82	?	Few days	Thyrototoxicosis.
9	3/24	Marked	?	10	0.6	82	82	0.20	½	Thyrototoxicosis.
45	7/24	Moderate	6	10	0.8	94	80	0.20	5	Thyrototoxicosis.
357	3/24	Marked	3	9.	1.6	64	84	?	2	Thyrototoxicosis.
360	10/24	Marked	6	11	2.4	80	78	0.20	1	Thyrototoxicosis.
190	4/24	Moderate	24	6	4.4	72	100	0.18	7	
869	5/24	Slight	1½	3	2.0	70	104	0.20	5	
184	11/23	Slight	6	2	1.6	64	72	0.18	1	
297	5/22	Marked	6	10	1.6	86	102	0.22	Few days	
266	7/21	Marked	12	5	2.0	72	100	?	1	
259	5/21	Slight	36	0	6.6	50	74	?	1	
166	1/23	Marked	8	10	1.6	72	84	?	½	
196	7/24	Moderate	2	7½	3.2	76	102	0.24	4	
358	8/24	Moderate	4	3	4.0	68	80	0.22	2	
359	10/24	Marked	24	6	2.4	58	64	0.22	1	
361	10/24	Slight	12	7	4.0	80	84	0.22	1	
362	10/24	Moderate	12	5	4.0	72	80	0.24	1	
363	11/24	Slight	12	3	5.6	48	52	0.26	1	
134	5/22	Marked	36	8	10.0	76	Unsuc	cessful		
178	4/23	Moderate	8	10	19.0	60	Unsuc	cessful		
330	7/23	Marked	2	10	15.0	56	Unsuc	cessful	Auricular flutter.
331	9/23	Moderate	4	6	17.0	70	Unsuc	cessful		
285	1/22	Marked	24	3	17.0	90	Unsuc	cessful		
265	5/21	Slight	6	8	4.2	72	Unsuc	cessful		
143	7/22	Marked	4	0	1.6	72	Unsuc	cessful		
148	8/22	Marked	24	9	5.0	76	Unsuc	cessful		
164	6/23	Moderate	3	3	5.0	64	Unsuc	cessful		
194	7/24	Moderate	48	6	6.0	72	Unsuc	cessful		
356	6/24	Marked	3	7	5.0	46	Unsuc	cessful	Auricular flutter.

there was a previous pathologic partial heart block which of course persisted after the resumption of the regular rate, and was independent of drug therapy; the other in which a prolonged conduction time had been maintained by the continuous administration of digitalis. It is noteworthy that those which quickly reverted to a fibrillation usually had the shorter *P-R* interval (Cases Nos. 129, 146, 11, 17 and 184). While the reverse is not altogether true, that the greater the *P-R* interval the longer the duration of the sinus rhythm, it so happens that in the cases in which the heart has remained regular for more than a year a markedly delayed conduction time was found to have been present (Cases Nos. 296, 368, 349 and 308). The significance of this observation is not to be emphasized, with respect to its prognostic value, until further observations can be made of all the factors concerned. The appearance of a prolonged conduction time after the restoration of the rhythm has been noted by others.^{6, 7}

There was no relationship in this series of cases between the amount of quinidin used to convert the rhythm (nor the amount of digitalis used previously) and the degree of heart block found to be present after the normal sinus rhythm had been established. It is quite remarkable that the total amount of quinidin needed to convert the fibrillation to a sinus rhythm in most cases was quite small. In only 2 of 41 successfully treated cases were more than 5 gm. of quinidin used, and in 25 cases not more than 3 gm. of the drug were used to restore the rhythm. It appears from this experience that the probability of success diminishes very rapidly after more than 5 gm. of the drug have been given.

Much has been written with regard to contraindications to the use of quinidin. Those usually heeded are: (1) Special sensitiveness to the physiologic action of the cinchona compounds; (2) a recent history of embolic phenomena; (3) marked decompensation of the heart. All cases on this service have been treated with the drug in which at least a moderate degree of compensation could be obtained, without regard to the duration of heart disease. In a few exceptional cases quinidin was given in the presence of a considerable degree of decompensation and with excellent results. There was but 1 case in this series to which the drug could not be given because of cinchonism, and in no case did the conversion of auricular fibrillation to the normal sinus rhythm give rise to signs of embolism. In 1 case (No. 129) it appeared that quinidin caused a respiratory paralysis which was fortunately transient. This patient was a man, aged sixty years, who during the administration of quinidin suddenly became unconscious, but gradually revived and his heart rate remained regular. Frey,⁸ among others, has reported a similar case.

In many instances it was difficult to determine definitely the length of time that fibrillation of the heart had existed before the

patient entered the hospital, but this factor is not regarded as of much prognostic value with reference to successful treatment. Many of the early papers on quinidin therapy emphasized the point that in long standing cases of fibrillation the normal heart rhythm could not usually be restored. The study of this series of cases does not substantiate that impression, and it seems that other factors than duration of fibrillation must play a part in the failure of treatment in this group of patients. Neither the kind of heart disease nor the amount of decompensation which the patient had experienced seemed to have any relation to success or failure of treatment so far as could be determined.

The maintenance of the sinus rhythm after its restoration by quinidin is a matter of the greatest importance because upon this depends the ultimate benefit which the patient may derive. Provided other things are equal, fibrillation in heart disease offers a shorter life expectancy than does a regular rhythm, and it usually curtails the patient's activities. In quinidin treatment more progress has been made, and less confusion exists, with regard to the actual restoration of the normal rhythm than to the maintenance of it, although the latter problem is of equal importance. The experience gained in the after treatment of this series of cases makes one feel not so sure that the administration of quinidin in the smallest effective dosage is the essential therapy in order to prevent the recurrence of fibrillation, as has been suggested.^{9, 10}

There was noted several times in the follow-up of the early cases in this series a succession of events as follows: The heart rate was lowered and the general circulation improved by the use of digitalis, and quinidin caused a restoration of the normal rhythm. The patient was allowed out of bed, quinidin continued in smaller doses, but no digitalis given. Then the heart rate gradually increased, and in a short time fibrillation of the auricles appeared. Experience so far seems to indicate that the use of digitalis in the after treatment of these cases is even more important than that of quinidin, but the problem is far from being solved. It is obvious that the use of digitalis tends to counteract and overcome the original factor which probably caused the auricles to fibrillate, namely, a weakened, diseased and overtaxed myocardium.

The accompanying table is made up of the essential information concerning the points which are emphasized in the paper. In some instances the time given for "probable duration of fibrillation" could only be estimated from the histories; many of the successfully treated cases we have been unable to follow in the metropolitan district of New York, and several cases have only recently been discharged from the hospital. The *P-R* intervals are those measured on Lead II of the electrocardiograms, and these were usually taken quite soon after the return of the normal mechanism. With few exceptions, electrocardiograms were taken of all

cases before and after the treatment with quinidin in order to detect the occasional appearance of auricular flutter with apparently regular ventricular rhythms, or when complete dissociation occurs with fibrillating auricles.

I am greatly obligated to Dr. Lewis A. Conner and Dr. Nellis B. Foster for their invaluable assistance in the study of these cases and in the preparation of the paper.

Conclusions. 1. The use of quinidin sulphate is justified and seems indicated in all cases of auricular fibrillation, except in those in which there are signs of recent embolism, marked decompensation of the heart or early appearance of the symptoms of cinchonism.

2. Both the temporary and permanent conversion of the fibrillation to a normal sinus rhythm by the drug seems to be favorably influenced by the presence of a delayed conduction time at the auriculoventricular junction.

3. The careful management of cases with regard to exercise, mental excitement and fever during quinidin administration greatly facilitates the favorable action of the drug.

4. The administration of quinidin is most effectual when given continuously through the day and night as suggested by the work of Lewis.

5. The use of digitalis to maintain the rhythm after its conversion seems to be even more important than that of quinidin in chronic auricular fibrillation.

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EXPERIMENTAL GASTRIC AND DUODENAL INFLAMMATION AND ULCER.

PRODUCED WITH A SPECIFIC ORGANISM FULFILLING KOCH'S POSTULATES.

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THE object of this paper is to give a preliminary report of my findings and to describe the morphology, isolation and recovery,



FIG. 1.—Guinea pig No. 105. Lesions confined to stomach. This animal received 2 cc. of toxin (intracardiac) and was killed by ether forty-eight hours afterward.

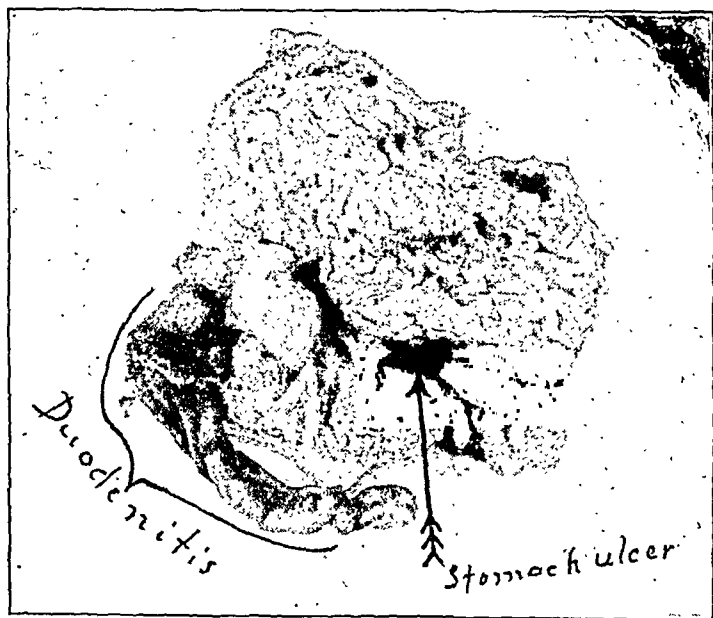


FIG. 2.—Guinea pig No. 3. Stomach and duodenum, showing ulcer in gastric mucosa and duodenitis.

cultural characteristics and pathogenicity, in the guinea pig, of an organism from the stomach contents of 2 patients, diagnosed as having gastric or duodenal ulcer, and from tonsil emulsion of a third patient, who also was diagnosed as having gastric or duodenal ulcer.



FIG. 3.—Guinea pig No. 102. Showing triangular ulcer at pyloric end of the gastric mucosa.

With material from these 3 known human ulcer cases I was able to reproduce lesions in the guinea pig, from which lesions the specific organism was isolated.



FIG. 4.—Guinea pig No. 17. Showing stomach with arrow pointing to minute perforating ulcer.

An injection of 5 cc of the stomach contents of Mr. H. (treated with 10 per cent sodium hydroxide, neutralized and suspended in saline solution) was made intraabdominally into guinea pig No. 1. The lesions diagnosed in the case of Mr. H. were reproduced in this guinea pig, and from these reproduced lesions the specific

organism was isolated. This organism was then injected, either in washings from agar slants or in glucose broth media (see table), into guinea pigs Nos. 2, 3, 4, 9, 10, 12, 16 and 17. This specific organism was subsequently recovered from the specific lesions in Nos. 2 and 3. No. 4, a small animal, died after eight hours; the specific lesions were reproduced in this instance, but an effort to recover the organism was not practicable. The specific lesions were also reproduced in Nos. 9, 10, 16 and 17. In the case of No. 12 the animal died of hemorrhage in the thorax. Pressure of other duties precluded any effort to recover the specific organism from Nos. 9, 10, 12 and 16. In the case of No. 17 I preferred not to disturb the specimen. Bacterial filtrate, forty-eight hours old, from the specific organism isolated from No. 1, upon being injected (4 cc intra-abdominally) into No. 11, also reproduced the specific lesions.

The specific organism recovered from No. 3 reproduced the specific lesions in No. 5, but was not in turn recovered from No. 5, the attempt not being made because of pressure of other duties. However, bacterial suspension (forty-eight hours old) from the bacillus that had been recovered from No. 3 reproduced in No. 6 the specific lesion, with myositis at the point of inoculation, which was done intramuscularly. The specific organism was recovered from the specific lesion in No. 6.

The complete tonsils of Mr. N. were emulsified with 10 per cent sodium hydroxide. The emulsion was neutralized and (after being washed with normal saline solution) 3 cc of it was injected intra-abdominally and intramuscularly in No. 7. In this animal the specific lesions were reproduced (with myositis), and the specific organism was recovered from these lesions.

Two cubic centimeters of the stomach contents of Mr. L. was injected intraabdominally and intramuscularly into guinea pig No. 8. The specific lesions were reproduced in this animal and the specific organism recovered from these lesions. The lesions were again reproduced in guinea pigs No. 13 (with the stomach contents of No. 8), 14 and 15 (with bacterial filtrate from No. 8).

Morphology and Cultural Characteristics. This organism varies considerably in morphology. The typical form (when stained by Gram's method) is that of fine slender rods with pointed or rounded ends from 0.1 microns to 0.4 microns in diameter by 0.5 microns to 3 microns in length. In the tissue the rods are so short that they resemble micrococci and comma-shaped bacilli, which are hardly visible. The various forms are often associated in the same culture. This organism is easily confused with a Gram-negative short-chain streptococcus at times.

Staining. The organism is Gram-negative and is stained by the ordinary anilin dyes, with the exception of a few whose staining power is faint. Therefore the morphology of the organism is not so easily established, owing to the varied actions of certain anilin

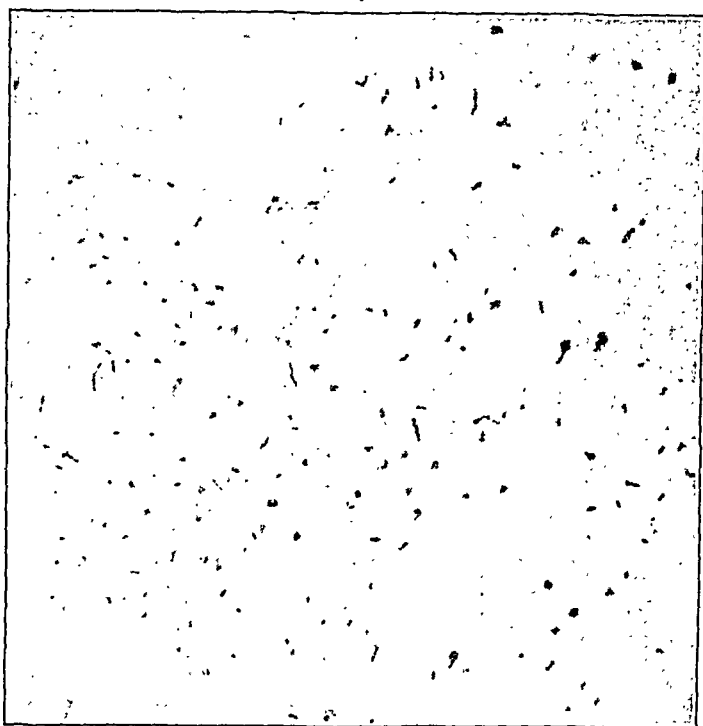


FIG. 5.—Specific organism, grown on nutrient agar for twenty-four hours and stained by Gram's method.

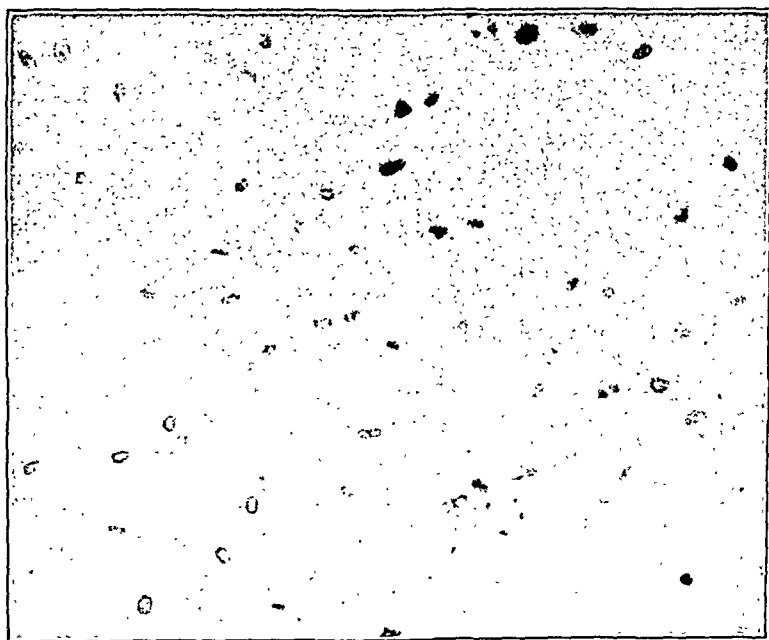


FIG. 6.—The same organism. Grown in glucose serum for six hours and stained by Bung's modification of Loeffler's method for flagella.

dyes, which on staining give the organism an entirely different aspect. When stained with Wright's stain it is faintly visible, resembling capsulated cocci. Under certain conditions the stained bacilli exhibit intracellular granules and bipolar bodies. They do not give the granulose reaction with iodine.

RESULTS OF EXPERIMENTS ON SEVENTEEN GUINEA PIGS.

Guinea pig No.	Weight before infection, gm.	Material injected.	Died.	Chloroformed.	Lived, days.	Necropsy.	Bacillus demonstrated.	Bacillus recovered.	Lesions reproduced.
1	480	Mr. H.; stomach contents; treated with 10 per cent sodium hydroxide; 5 cc suspect material, intraabdominally	×	0	17	Duodenitis and ulcer of stomach	×	×	×
2	500	Bacillus isolated from No. 1; 3 cc bacterial suspension, intraabdominally	×	0	16	Duodenitis and ulcer of stomach	×	×	×
3	300	Bacillus isolated from No. 1; 1 cc bacterial suspension, intraabdominally	0	×	6	Duodenitis and ulcer of stomach	×	×	×
4	200	Bacillus isolated from No. 1; $\frac{1}{2}$ cc bacterial suspension, intraabdominally	×	0	8 hrs.	Duodenum and stomach are hemorrhagic throughout	0	0*	×
5	515	Bacillus isolated from No. 3; 1 cc bacterial suspension, intraabdominally.	0	×	30	Duodenitis	×	0*	×
6	445	Bacterial suspension (48 hrs. old), bacillus isolated from No. 3; 2 cc intramuscularly.	0	×	17	Myositis and duodenitis	×	×	×
7	450	Mr. N.; tonsils, extracts from (treated with 10 per cent sodium hydroxide); 3 cc intraabdominally and intramuscularly	0	×	10	Myositis and duodenitis	×	×	×
8	780	Mr. L.; stomach contents; 2 cc intraabdominally and intramuscularly	×	0	25	Duodenitis and ulcer of stomach	×	×	×
9	600	Bacillus isolated from No. 1; 2 cc intraabdominally	0	×	25	Duodenitis	×	0*	×
10	525	Bacillus isolated from No. 1; 2 cc intraabdominally	×	0	11	Duodenitis and ulcer of stomach	×	0*	×
11	400	Bacterial filtrate (48 hrs. old) from bacillus isolated from No. 1; 4 cc intraabdominally	×	0	20	Duodenitis and ulcer of stomach	0	0	×
12	650	Bacillus isolated from No. 1; grown for 48 hrs. in glucose broth media; 4 cc intraabdominally	×	0	1	Hemorrhage in thorax	0	0*	0
13	675	Stomach contents from No. 8 guinea pig; $1\frac{1}{2}$ cc intraabdominally	0	×	15	Duodenitis	×	×	×
14	240	Bacterial filtrate (48 hrs. old) from bacillus isolated from No. 8; $\frac{1}{2}$ cc subcutaneously	0	×	19	Ulcers in duodenum and stomach	0	0	×
15	265	Bacterial filtrate (48 hrs. old) from bacillus isolated from No. 8; 1 cc intraabdominally	0	×	19	Ulcers in duodenum and stomach	0	0	×
16	240	Bacterial culture (48-hr.-old broth culture) from bacillus isolated from No. 1; 1 cc intraabdominally	×	0	6 hrs.	Hemorrhagic areas in duodenum and the stomach	0	0*	×
17	240	Bacterial culture (6-hr.-old broth culture) from bacillus isolated from No. 1; $\frac{1}{2}$ cc intraabdominally	×	0	20	Perforated stomach ulcer	0	0*	×

* No effort made to recover; see text.

Biology. It is an aërobic, nonmotile bacillus, and grows best at 30° to 37° C., and does not form spores. It grows readily on the usual culture media. The colonies upon agar are at first grayish-white, semitransparent, slightly raised and fimbriated. They have a very striking cultural characteristic (on agar), which is the complete disappearance of all the colonies after a certain period of incubation has elapsed, leaving in their places a highly refractive transparent film. Gelatin is liquefied, forming a crateriform stab at first. In glucose broth there appears a flocculent turbidity with subsequent formation of thin pellicles and grayish sediment. If the growth is left undisturbed in liquid media, pellicles will form. In inulin serum media there is a tendency to capsule formation. In saccharose, mannite, dextrose and neutral-red serum media the bacillus produces acid and does coagulate serum. Neutral red produces slight fluorescence. There is only a weak acid production in maltose, inulin and lactose. Russell's double-sugar media is acid in the butt and alkaline on the slant. Colonies grown on lead-acetate media are brownish-black in stab, while on the slant they are brown, with dark brown centers and crenated contours. The morphology varies in the different sugar media.

Pathogenicity. Guinea pigs inoculated with the specific organism, intraabdominally or intramuscularly, showed lesions in the duodenum or stomach, or both, in which the bacillus was demonstrated (see table). Following this I had no difficulty in culturing the organism in such lesions or from points of inoculations. It has already been shown that with this recovered bacillus I was able to reproduce similar lesions in other guinea pigs.

If given small doses (0.5 to 1 cc) the animals survived from six hours to four weeks. On the other hand, 3 cc of a forty-eight hour culture killed a large guinea pig within twelve hours, with typical symptoms of toxemia starting with convulsions and leading to gradual paralysis and death. The regions involved were the duodenum and stomach, both showing striking inflammatory reactions and hemorrhagic areas. In the course of these subsequent experiments I was able partially to protect another pig by giving 2 cc of rabbit blood serum (the rabbit was partially immunized with the organism) after the onset of the first symptoms which occurred after one hour. The animal seemed to improve at first, but grew gradually worse, and six days later I observed profuse bleeding from the rectum. The animal was chloroformed. Necropsy revealed necrosis at the point of inoculation and slight myositis in the right hind leg, being the side on which injection was done. In the abdominal cavity there were no lesions of any kind. The duodenum, however, had six small, almost perforated, inflammatory ulcers surrounded by white rings. The stomach revealed one large ulcer, from which blood was still oozing. Another pig inoculated at the same time, but given an equal mixture of the serum (3 cc

and broth culture 3 cc., which stood for ten minutes before inoculation) remained in perfect health. The sterile broth filtrate (the organism had been grown in broth media for forty-eight hours) produced duodenitis and ulcers of the stomach after twenty days in the same manner as the organism itself. Secondary invaders, namely streptococci and other organisms, also could be readily demonstrated. My experiments indicate in the case of the specific organism that washings from agar slants are not very toxic to guinea pigs, though rabbits inoculated intravenously with dead cultures showed within a few hours grave symptoms of toxemia, which lasted for days without much improvement. Three cubic centimeters of broth culture (intraabdominally) proved fatal within twelve hours to a rabbit weighing 8 pounds.

The intravenous injection of 2 cc of a suspension grown in Rosenow's¹ glucose brain media proved fatal within two hours to a rabbit weighing 7.5 pounds. There were hemorrhagic areas throughout the stomach and very marked lesions at the pylorus.

In view of these findings, I consider that ulcers of the duodenum and stomach may be due to a specific organism.

Conclusions. 1. From the experimental work in question, it would appear that there is a specific organism which exercises a selective affinity for the stomach and duodenum, and that it tends to produce ulcers in these localities.

2. Material taken from human beings diagnosed as suffering from gastric or duodenal ulcers, or both, when injected into guinea pigs, produced in the animals with great regularity either marked duodenitis or ulcers, or both. (In 2 cases in which the injection had been made intramuscularly there resulted duodenitis and myositis.)

3. From these lesions in the guinea pigs scrapings have been taken, the specific organism recovered therefrom, and on reinjection in pure culture in other guinea pigs it has produced similar lesions.

4. Mixed infections were sometimes found at the site of the ulcer, but the specific organism described was recovered (if it had been originally present in the material injected) every time the attempt at recovery was made.

5. Sterile filtrates of the specific organism (grown in the broth media for forty-eight hours) produced the same lesions as the organism itself.

NOTE.—These experiments were made possible through the courtesy and collaboration of the Clinic Staff of the Johnston-Wickett Clinic, Anaheim, California.

¹ Med. Clin. North America, Mayo Clinic, September, 1921.

THE SIGMOIDOSCOPIC PICTURE OF CHRONIC ULCERATIVE COLITIS (NON-SPECIFIC).

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As time passes, we are becoming more and more familiar with the recognition of the course, pathology and the treatment of the malady which is identified under the name of idiopathic ulcerative colitis, simple ulcerative colitis, colitis gravis (Rosenheim), or chronic ulcerative colitis of the nonspecific variety. At this moment we are excluding from discussion the specific varieties of ulceration of the colon, such as amebic colitis, specific dysentery due to any one of the various types of bacillus dysenteriae, diphtheritic colitis, or forms of chronic infection of the colon due to parasitic invasion. The discussion of the nonspecific form of ulcerative colitis restricts itself to those cases in which no recognized microorganism can be identified as the offending factor. It deals with a subacute or chronic disease characterized by a chronic inflammation of the mucous membrane and walls of the large intestine, in the pathologic picture of which ulceration predominate. The course is in most cases a chronic one, extending over months and years, not always or often a continuous one, but one that is punctuated by long periods of remission followed by severe and repeated recurrences of all of the symptoms. Fever, malaise, prostration, protracted and persistent diarrhea with some tenesmus and the passage of blood, mucus and pus, characterize the progress of the case. The course is usually rapidly downward; a loss of strength and weight is the rule, the loss of flesh extending up to 40 to 60 pounds in a period of a few months. An advanced secondary anemia occurs in severe cases, exceptions to which rule are few in number. The severity of the disease is well indicated by the name "colitis gravis," given to it by Rosenheim, indicating that chronic invalidism or death is a greater probability than recovery. By the same token the unsatisfactory status of the previous methods of therapy is most clearly indicated.

In the current literature the factors of etiology, symptomatology, the clinical course and prognosis have been ably described and summarized. Most thorough descriptions of simple ulcerative colitis have been published by Albu, Schmidt, Yeoman, Logan, and quite recently by Lynch and Felsen. These papers have covered series of cases which for this disease, in the experience of any one

person, have been fairly large, Logan's publication in 1919 revealing the unusually extensive collection of 117 cases. To the classic description of the disease given by these various authors we can add but little; we have devoted our attention to the field of therapy and the sigmoidoscopic picture of the healing colon.

During the years 1921 to 1923 inclusive we have observed at the Mount Sinai Hospital a series of 29 cases. Careful sigmoidoscopic examinations have been made in all instances, not only as an indispensable means of establishing a diagnosis or of observing the pathologic picture, but repeated sigmoidoscopies have been liberally used to check up the results of our various therapeutic endeavors.

NOTE.—A short word of warning should be issued on the possible dangers of the use of the sigmoidoscope. In even the most experienced hands a rupture of the rectum or sigmoid is possible. It has happened to even the most able men. The instrument must be introduced slowly and *under control of the eye*. Undue force exerted at any point is to be avoided. In instruments in which an air bulb is used as an inflating device the avoidance of too much pressure within the rectum is absolutely essential. A rupture of the intestine, of the sigmoid or of the rectum must be followed by an immediate laparotomy with suture of the rent. If this be done little evil consequence can follow. If time is lost or any other method is attempted to cover over or hide the accident a fatality will probably, if not surely, ensue.

The Pathologic Picture. The process of ulceration and inflammation that characterizes the disease is one which may involve the whole or some of the segments of the large intestine. In the milder cases only the rectum, or the sigmoid, or both may be involved. In the severer cases, particularly those of long standing, the entire colon from rectum to cecum, and even a small stretch of the terminal ileum may be the seat of the disease. It has been claimed that the disease may affect only segmental areas of the large intestine, such as the descending colon or the cecum. If so, we have not observed such cases, for in all the instances in which the disease has led to death, the autopsy has revealed almost universal ulceration of the entire large intestine, from anus to cecum and even to ileum. These cases, of course, have evidently been examples of the most severe and fatal form of the disease. In 1 case in which cecostomy was performed the laparotomy revealed a gut which was so indurated with inflammatory exudate that the entire colon felt like a rigid tube, all pliability having disappeared. Upon lifting the sigmoid the entire descending colon rose with it; the same applied to the ascending colon on the right side. On the other hand, in the milder cases, particularly those that run a subacute course, the pathologic process seemed restricted to the rectum and pelvic colon, since in passing the sigmoidoscope upward it was

seen that the brunt of the force of the disease was expended on the lower rectum, particularly that section of the ampulla of the rectum which directly adjoined the internal sphincter. The valves of Houston come in for a large share of the injury, the lower fold particularly being commonly the seat of the largest and most extensive ulcerations.

In one of our cases the colitis was observed to follow the spontaneous rupture of a rectovaginal abscess, the latter occurring as a sequel to a streptococcus tonsillitis, with erythema nodosum and a purpuric rash as concomitant symptoms. The rectovaginal abscess ruptured into both cavities, leaving a permanently communicating fistula. The ulcerative colitis followed shortly and has remained for several years, being lighted up from time to time by fresh attacks of tonsillitis and erythema nodosum. Other cases have followed both internal and external hemorrhoids, probably with secondary infection. It would thus seem that not only is the rectum the most frequent portal of entry for the infection, but that the initial pathological lesion is resident in the rectal ampulla and anal canal, spreading from there upward as far as the sigmoid in the milder cases, and depending upon the duration and severity of the process as far as the transverse or ascending colon or cecum in the graver cases. This point is of importance not only because it bears upon the etiology of the disease but insofar as it furnishes the rational basis for the treatment by means of rectal irrigations applied from below upward. It again explains why in those cases which come earliest for treatment the best results are obtained by antiseptic nonirritant lavages, for the disease is still limited in the early stages to the lower segments and is thus within reach and amenable to our therapeutic efforts.

The Sigmoidoscopic Picture. The instrumental observations which we have made of ulcerative colitis are similar in all respects to the careful descriptions furnished in the recent publications of Yeoman and of Lynch and Felsen. We may, however, classify the various stages of the disease as observed through the sigmoidoscope into: (1) Acute or subacute stage; (2) the active chronic stage in which the disease is six months to two years or more in duration; (3) the later chronic nonhealing ulcerative stage; (4) the terminal picture characterized by polyposis of the colon or colitis polyposis cystica (Virchow). As late sequelæ, one may infrequently observe fibrous stricture of the rectum, and in one instance malignant degeneration of the polypoid state into frank carcinoma of the rectal ampulla.

These various stages may be observed by careful studies of the sigmoidoscopic picture at intervals of the disease. Even the earliest stages of polypoid formation may clearly be seen through the sigmoidoscope when one is acquainted with the pathologic process. In addition, one may observe the stages of regression

of the process, under successful therapeutic onslaughts; the disappearance of the superficial ulcerations in the subacute cases and the subsidence of the granular and ulcerative forms in the more chronic types.

The Acute or Subacute Stage. The sigmoidoscopic pictures of the early phases of the disease are characterized by the appearance of marked hyperemic congestion of the mucous membrane; the mucosa is in a stage of active inflammation, red, often fiery red, the venules dilated, the whole mucosa friable and bleeding wherever the instrument impinges upon the wall of the gut. Superficial ulcers varying from pin-head size to those larger ones 1 or 2 cm. in diameter dot the entire visible mucosal area. The hemorrhage from even these small ulcers may be so excessive as to resemble blood squeezed from a sponge. Here and there a deeper punched-out ulcer is seen, usually occupying the lower reaches of the rectal ampulla and most commonly situated on one of three folds of Houston, the lower fold being the most frequently involved. The number of ulcerations may vary from a few or up to hundreds. At times older and larger ulcers are situated at the rectosigmoid angle or in the lower portions of the pelvic colon.

The whole mucosa is covered by a mucoid exudate, which in the later stages become purulent. In cases of unusual severity one may note large areas covered by a fibrinous or fibrinopurulent membrane, which resembles the pseudomembranous deposit of a severe pharyngitis or of a diphtheritic tonsillitis. This membrane is more or less strongly adherent; at other times it is easily frayed by the passage of the instrument over it, leaving an eroded bleeding surface.

In 1 case of a fulminating type, with a temperature of 104° F. and extreme prostration with almost incessant diarrhea, the picture was described as consisting of deep jagged irregular ulcers, bleeding freely and extending from the internal sphincter as far up as the instrument would reach (30 cm.). The ulcers could be easily palpated through the anus, covering the lower fold of Houston on the lateral walls of the rectum. The whole makes the impression as of "raw beef," the superficial mucosa having been entirely exfoliated, leaving the raw tissues of the deeper layers exposed. Ruge, in 1907, described 75 cases which he termed purulent and ulcerative proctitis. In this series he emphasized the type of cases in which purulent inflammation rather than ulcers predominated. He considered the disease as one of proctitis rather than of colitis, a conception which is probably not correct, but one which rightly stresses the point that the origin and center of the pathologic process resides in the rectum and lower colon.

The Active Chronic Stage. This refers to those cases in which the disease has been actively present, giving clinical symptoms for from six months to two years. This picture is similar in many respects

to the above, but represents a less acute stage of the disease with a more advanced and progressive lesion. The severe acute inflammatory congestion is less marked. On the other hand, ulcers are more numerous, are deeper, more irregular and extensive in diameter and appearance. The walls of the ulcer are less undermined and more discrete than is seen in amebic colitis. It is only in the severer and in the fatal cases, such as come to autopsy, that one sees the entire mucosa replaced with sinuous or transversely linear ulcerations that merge the one into the other and that burrow under the mucosa until the entire submucosa is exposed. One sees in this chronic and active stage of the disease the picture of severe ulceration; between the ulcers the mucosa is heaped up and hypertrophic, friable, sanguinous. The whole lumen of the gut is often filled with fresh red or older black (clotted) blood. The discharge from the surface consists of thick glairy mucus or of mucopus; at times a free purulent exudate is discharged from the anus, causing an irritative perianal dermatitis. Not infrequently suppurative condylomata appear around the margin of the anal ring, these consisting of raised papilloma-like acuminate outgrowths. External hemorrhoids are practically never absent and are a logical sequel to the constant pressing and straining incident to ten to twenty stools per day.

The Late Hypertrophic or Granular Stage of the Disease. This phase is seen as a later stage of the above process, a stage in which the active inflammatory period is accompanied by a granulating less active, more indolent reaction. It may last for many years and may be present during the periodic exacerbations of the course that characterizes the prolonged clinical picture.

The sigmoidoscopic picture of this stage is characterized by a persistence of ulcerations, some of them small and scattered, others again numerous, larger, irregular, deep and heaped up indurated inflammatory borders. This picture is to be recognized by the fact that the stage of intensive ulceration in the depths is replaced by one of a proliferative hypertrophic and granulating reaction. The ulcer walls themselves are more raised and thickened than deep. The mucosa between the ulcers is thrown up into hypertrophic villous-like folds. Multiple ulcers in the submucosa may be seen separated by bridges of hypertrophied mucosa which in many places are so thickened that they resemble polyps with sessile bases. In other areas more free from ulcers, or in places where superficial ulcerations have undergone retrogression, the mucosa may appear less congested, grayish-pink in color, the surface being granular and uneven, giving the appearance as if dotted with swollen tapiocal granules. This is the stage of chronic granular or follicular colitis and represents a later and less active or indolent stage of long standing inflammation. It may also be present and persist to a degree during those months or years in

which the disease passes into an intermission period with general freedom from active symptoms but with a persistence of 1, 2 or 3 semisolid stools passed with some urgency, usually in the morning. As such it may assume the type of matutinal diarrhea, or again of orthostatic diarrhea (diarrhea on assuming the erect position). The patient at this period may think himself apparently well; he is at least comparatively free from symptoms, may resume his, or more frequently her, occupation, and may retain his weight or even recover some of the excessive loss of flesh that is incidental to the more active stage of the disease. The granular colitis may be present as the sole remnant of a previous ulcerative stage or may be part of the picture only of a more severe hypertrophic reaction. Coincidentally areas may be seen, where the mucosa is pale and smooth and somewhat shiny, with newly formed arterioles visible, traversing the healed or healing areas of mucosal tissue. In the late stages, particularly where spontaneous healing is taking place and the clinical phenomena are all subsiding, the only sigmoidoscopic picture may be one of a dry glazed mucosa, granular and uneven in appearance, covered by strains of glairy mucus. Ulcers are no longer visible.

Polypoid Colitis. When the disease extends more or less actively over many years, showing little or no tendency to spontaneous healing, one may observe a final stage, a stage which is characterized by the great predominance of the hypertrophic or regenerative element running hand-in-hand with the persistence of indolent or partially healed ulcerations. Cases of colitis, or of chronic "dysentery" with polypoid excrescences had been described in the literature as early as 1721 by Menzel and in 1832 by Wagner. Rokitsansky described the mechanism by which such proliferative processes are formed. He attributed the origin of the small excrescences seen in cases of healed or healing colitis to small islands of persisting mucous membrane that remained after the ulcerative process had ceased. The polyps formed on the edge of ragged margins of healing ulcers. Virchow elaborated the description of this polypoid degeneration of the inflamed mucosa in cases of colitis; he described the polyps as being vesicular fluctuating prominences scattered over the surface of the mucosa. The surface of these polyps was often depressed; from them could be expressed gelatinous mucoid material which apparently had accumulated in the dilated crypts of Lieberkuhn which composed the stalk and body of those newly formed excrescences.

One may add to this description the contribution of Hewitt and Howard who advanced the idea that since at least in the upper colon the polyps seemed to be situated at the line of the entry of the blood supply, namely, the mesenteric attachment, that therefore the polyps arose from areas of tissue which because of their better vascularization had withstood the ravages of the destructive

ulcerative process. The resultant increased blood supply to these surviving shreds of tissue resulted in active hyperplasia of the mucous glands and submucous connective tissue with consequent polyp-like formation. A secondary contraction of the proliferated fibrous tissue resulted in occlusion of the tubules at their bases and retention of the mucous contents to form a cyst. As the tissue at the base contracted, the proliferated hyperplastic tissue stood out more and more until a well-defined polyp appeared over the surface of the mucosa.

Thus the stage of polypoid colitis may take place as part of the picture of an old chronic colitis of long standing but with healing tendencies. The initial stage of polypoid colitis was seen by us through the sigmoidoscope in 1 of our cases, all the different elements in the process being readily distinguishable. Or the polypoid appearance may be the sole remnant of a healed colitis in which the ulcers have disappeared and the healing of the mucous erosions advanced to a terminal stage.

As final complements of long standing ulcerative colitis, we have observed in 2 cases well defined stricture formation of the lower reaches of the rectal ampulla. The area about the lower valve of Houston, and particularly between that fold and the internal anal sphincter seems to bear the brunt of the disease, since it is to this point that the irritating mucopurulent secretions are swept. Gravity alone would cause the collection of such fluid or semifluid material to collect in this area. The result is deeper ulcers at this location, ulcers that penetrate through the submucosa and probably involve the powerful underlying muscular bundles of the levator ani and similar constrictor muscles. As these ulcerations tend eventually to heal there is a constant tendency to scar and stricture formation, the end result of which is readily distinguishable with the palpating finger. The thickened lowermost valve of Houston often forms the base of the obtruding scar-tissue diaphragm.

Such a stricture-forming process may be felt even in an earlier stage in many cases of ulcerative colitis; it is quite characteristic of this particular pathological process.

Finally, we have observed in 1 case a malignant degeneration of the late stage of a polypoid ulcerative colitis, with the frank occurrence of a carcinoma of the rectal wall. In brief, this was a case of a nonspecific ulcerative lesion of the colon, fourteen years or more in duration. Many years previously a cecostomy had been performed for the relief of symptoms. The relief afforded was disappointing, the symptoms continuing on and off with practically no intermission during the entire period. The polypoid stage of the disease was already in evidence ten years ago. More recently the patient again came under observation with renewed symptoms of his disease. The sigmoidoscopic examination revealed an

extensive polypoid colitis, in addition to which one observed on the left lateral wall of the rectal ampulla, growing in a mass of polyp-like excrescences, an ulcerating massive neoplasm. Sections removed for histologic examination showed the presence of adenocarcinoma.

The value of this observation lies in the fact that the individual was under the observation of one of us for various periods during the entire course of the disease, all the stages being more or less observed during the frequent admissions of the patient to the wards of Mount Sinai Hospital. It is obvious that the carcinoma of the rectum might have occurred as an incident without relation to the presence or absence of such a chronic inflammatory lesion. But it is more natural as well as logical to connect the two facts and attribute the occurrence of an adenocarcinoma of the rectum to a malignant degeneration of a polypoid colitis under conditions of continued and long standing inflammatory traumatic insult.

Multiple polyposis of the colon as a primary condition independent of ulcerative colitis has been extensively described by Doering and recognized by Lockhart-Mummery. He collected from the literature 50 cases in 24 of which (46 per cent) malignant carcinomatous degeneration had taken place. The great tendency to cancerous development on such a basis is a conceded fact. It is, therefore, not surprising that a similar malignant change should have been observed in the terminal polypoid stage of ulcerative colitis.

Summary. The pathologic areas involved in cases of non-specific ulcerative colitis may be distributed throughout the course of the colon, or in patches.

According to the sigmoidoscopic picture one recognizes progressive stages such as:

1. Acute or subacute stage.
2. Active chronic stage.
3. A later granular ulcerative stage.
4. Terminal picture of colitis polyposis cystica (Virchow).
5. As sequelæ one may occasionally see mild stricture formation or a carcinomatous degeneration of the polypoid state.

The stage of healing may be extremely rapid, so that the regressive or reparative process may change an ulcerative hemorrhagic area into a healed mucous membrane within a few weeks.

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THE POSSIBLE RELATIONSHIP BETWEEN GUANIDIN AND HIGH BLOOD PRESSURE.*

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THE thought that arterial hypertension is produced by some undiscovered or unstudied product of metabolism has often been expressed. Some writers have suggested that the overproduction of some substance may be responsible for the production of high blood pressure, while others, with the picture of chronic nephritis and its impaired excretion in mind, have thought of the retention of some substance as the causative factor in arterial hypertension.

As a contribution to this subject we began about eighteen months ago a systematic study of the pressor effects of various substances present in the normal urine. One of the substances studied, methyl guanidin, has such powerful and prolonged pressor effects as to suggest that it may be at least one of the metabolites concerned in the production of high blood pressure.

Methyl guanidin was first demonstrated in the urine of normal persons by Kutcher and Lohmann, in 1908, and has been subsequently studied, particularly by Noël Paton and his co-workers, who assert that it is the toxic substance responsible for the production of tetany.

In our experiments we have used methyl guanidin sulphate, methyl guanidin nitrate and also dimethyl guanidin sulphate, guanidin carbonate, guanidin thiocyanate and guanidin hydrochlorid. All of these guanidin compounds show a very striking ability to raise the blood pressure and to maintain it at a high level. Following the intravenous injection of 0.1 gm. to 0.2 gm. of methyl guanidin sulphate per kilo of body weight the blood pressure in dogs is often doubled or even tripled, this high pressure persisting often

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from four to five hours. Similar results have been obtained following intramuscular injection and from administration through a stomach tube. Larger doses usually produce a fall in blood pressure, accompanied by paralysis of respiration, irregular heart action and twitching or convulsions similar to those observed in tetany.

We have also studied some of the features of the mechanism by which this high blood pressure is produced. Section of the vagi, after injection of the guanidin compounds, has no effect on the high blood pressure, and if both vagi are cut before injection the blood pressure rises just as in normal animals. In the decerebrated dog, whose medulla is destroyed, injection of methyl guanidin still produces an elevation in blood pressure. We have also noted a marked blanching of the ears of rabbits following injection, and in studying the retinal arteries with the ophthalmoscope we have actually seen a constriction of the arterioles following injection of guanidin compounds. These observations suggest that a peripheral constriction of the arterioles is responsible for the elevation in blood pressure, an experimental observation in harmony with much of the best thought on the mechanism of the production of hypertension in man.

The next phase of our work was to study the urinary secretion of the guanidin bases in normal individuals, in dogs with experimental uranum nephritis and in patients suffering from chronic nephritis and essential hypertension. The most satisfactory method we have used has been that of Findlay and Sharpe, the principle of which is the removal of proteins by tannic acid and the precipitation of the guanidin bases with picric acid in the form of dimethyl guanidin picrate. This method does not change creatin or creatinin into guanidin, which apparently happens in some of the other methods where mercury salts are used.

A study of the urinary excretion of the guanidin bases in normal individuals has shown considerable daily variations, as is the case with some of the other nitrogenous substances, but most normal individuals have shown an average of 100 mg. per day. In experimental uranum nephritis, and in chronic nephritis with hypertension, the daily excretion of the guanidin bases has uniformly shown a decrease when compared with normal individuals, the curve of guanidin excretion following roughly the curve of nonprotein nitrogen excretion. In essential hypertension we have usually found a diminished excretion of guanidin, although this has not been constant.

We have recently studied the excretion of guanidins in 2 patients with essential hypertension, admitted to the hospital with marked myocardial insufficiency, edema and poor urinary excretion. The patients were treated with digitalis and diuretin, the blood pressure fell markedly, the urinary secretion was markedly increased and there was a very marked increase in the excretion of guanidin

bases. These observations suggest a retention of the guanidin bases during the period while the blood pressure was so high.

The methods that have been used for the determination of the blood guanidins up to the present time have been so time-consuming, and have required such large amounts of blood for the determinations, that they have not found much clinical application. The colorimetric method devised by Marston represents an important step toward the solution of this problem.

The addition of Marston's reagent to an aqueous solution of guanidins produces an intense red color which can be used for a colorimetric determination. Pure creatin or creatinin gives no reaction and urea shows no color until a concentration of 500 mg. per 100 cc or greater is reached. The addition of this reagent to blood serum, diluted with distilled water, or to an aqueous extract of certain tissues gives a red color which is increased when guanidin compounds in very small quantities are added. Marston has pointed out that ammonia and uric acid may interfere with the reaction if their concentration is high and the amount of guanidin very small.

We have examined the blood serum of a large number of normal individuals and of patients suffering from arterial hypertension, but have found no increase in guanidin in the blood of patients with high blood pressure. This has led us to a further study of the blood guanidins of dogs after the injection of guanidin compounds, and we found that while the guanidin content of the blood is increased for two or three minutes after injection, this excess has largely or entirely disappeared in five minutes, although the blood pressure continues elevated for four or five hours.

Such findings suggest certain possibilities: Rapid excretion of guanidins, storage in some tissue, transformation into some other substance which has a prolonged pressor effect, or rapid saturation with destruction of the excess.

The urine after injection of guanidin compounds shows, however, no constant increase in guanidin bases, and removal of both kidneys, excluding the possibility of urinary secretion does not prevent the rapid disappearance of guanidin from the circulation. The guanidin content of the muscles, lungs, liver, heart, brain, spleen and kidneys after injection with guanidin bases is apparently no greater than that of normal controls. When we consider the possibility of guanidin being changed into some other pressor substance, a study of its chemistry would indicate that it is probably either transformed directly into urea or first into cyanamid and then into urea. We have studied the action of both urea and cyanamid and neither has any pressor effect.

These observations have led us to the view that the pressor effect of the guanidin compounds is apparently exerted almost immediately on the neuromuscular apparatus of the smaller bloodvessels. It is

probable that these tissues fix a certain amount of guanidin and the excess is very rapidly destroyed.

In addition to the study of the pressor action of guanidin, we have studied the effect of certain substances on the hypertension produced by guanidin. *Veratrum viride* and amyl nitrite produce only very transient effects upon this high blood pressure. Calcium chlorid, on the other hand, produces a permanent fall in blood pressure accompanied, however, by marked cardiac irregularity. When an equal quantity of potassium chlorid is added to the calcium chlorid a prompt fall in blood pressure without cardiac irregularity results, this fall being produced by either intravenous or intramuscular injections. If calcium chlorid and potassium chlorid are injected before guanidin compounds no rise in blood pressure occurs. This indicates a chemical action of these substances, neither of them having any marked effect upon normal blood pressure when injected in doses as large as those which will reduce the high blood pressure following the injection of guanidin. We have also produced a similar fall in blood pressure by the use of normal hydrochloric acid and ammonium chlorid.

Some very interesting results were obtained with the parathyroid extract of Hanson and of Collip. Both of these extracts reduce very promptly the hypertension produced by injection of guanidin compounds. It has also been noted that the blood calcium, following injection of the guanidin compounds, fell and then rose following injection of the parathyroid extract. While the blood calcium was low the blood pressure was high, and as the blood calcium rose the blood pressure fell. We also found that certain other organ extracts, particularly that of the liver, lowered the blood pressure which had been elevated by guanidin compounds.

Summary. These observations suggest there may be a relationship between guanidin and arterial hypertension. The question is left unanswered as to whether high blood pressure is caused by an increased production of guanidins due to an error of metabolism, or due to a faulty excretion of guanidins by a damaged kidney. Our observations indicate that any great excess of guanidin is destroyed, although a part of this excess may be retained, probably fixed by the neuromuscular apparatus of the smaller bloodvessels with the production of an arterial hypertension.

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CALORIMETRIC STUDIES OF THE EXTREMITIES FOLLOWING LUMBAR SYMPATHETIC RAMISECTION AND GANGLIONECTOMY.*

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THE experimental and clinical work of Royle and Hunter on ramisection for spastic paralysis has awakened interest in the physiologic effects. The object of their experimentation was to confirm the work of Boeke, de Boer and Langelaän, with regard to the influence of the gray rami on the plastic tone of striated muscle. Being convinced that the gray rami play an important part in maintaining plastic tone, Royle applied the procedure, ramisection of the gray rami, to patients with spasticity and found that it diminished the plastic tone. He observed in 1 patient a change in temperature, the extremity operated on being warmer

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to the touch than the one not operated on. Absence of sweating was also noted in the leg on the operated side in 1 patient. In view of this phenomenon, we believed it particularly important to study carefully the vasomotor effects on the extremities in cases in which ramisection had been done. We have attempted to carry out such studies in relation to skin temperature, heat production and radiation of the lower extremities before and after operation in 5 cases of spastic paraplegia.

Operative Procedure. Inasmuch as we decided to perform a bilateral lumbar ramisection, we employed a median-line incision extending from the symphysis to a point 7.5 cm. above the umbilicus. The patient was placed in the Trendelenburg position, and the intestines were displaced upward by a pack. The posterior wall of the peritoneum was incised on the right side along the margin of the inferior vena cava and the right common iliac vein. The dissection was then carried down to the mesial border of the psoas muscle, retracting the ureter outward and the inferior vena cava mesially, exposing the lumbar sympathetic trunk and ganglia with the gray rami, passing along with the intervertebral vessels to communicate with the spinal nerves at the intervertebral foramina.

Royle advocated only the division of the rami, but we have learned that it is possible also to remove the second, third and fourth lumbar sympathetic ganglia with the sympathetic trunk without any serious complications of the hypogastric plexus. This procedure was employed in the 4 cases reported. The technic for the left side is similar to that for the right, except that if the sigmoid is firmly fixed in the left iliac fossa it is necessary to mobilize it by opening the peritoneum laterally to the sigmoid attachment; after this it may be elevated and displaced mesially, again exposing the ureter, retracting it outward and elevating the lower portion of the abdominal aorta and the common iliac artery, thus exposing the sympathetic ganglia, trunk and rami, which may then be removed as on the right side, making sure to divide the sympathetic trunk above the second lumbar sympathetic ganglia and below the fourth lumbar sympathetic ganglia.

Postoperative Caloric Changes. In order to determine the possible effects of this operation on the vasomotor nerves, the following plan of study was carried out in part or in whole before, and for variable periods after, operation.

1. Skin temperature determinations were made by means of the Tycos self-recording temperature apparatus under controlled conditions of room temperature and position, with uniform observation periods.

2. Calorimetric studies were made of heat production in the feet by means of the Stewart-Kegerreis calorimeter,^{1, 3} under carefully checked and controlled conditions with regard to rest, and constant

room temperature. The basis of calculations of heat transference is given in small calories, each minute for each square inch of surface area.

3. Clinical observations were made relative to the subjective symptoms of the patient, color of the skin, behavior of the sweat glands and blood pressure readings. The time relationship is shown in Tables I and II. There was considerable difficulty in attempting to control muscular movement in the period following operation. These estimations were made at the bedside and controlled as far as possible.

Case Reports. CASE I.—The skin temperature determinations were made on the inner side of the thighs, the outer portion of the middle part of the legs and the palmar surface of the feet. The readings before operation showed a decreasing temperature toward the periphery; the afternoon following operation sharp increases were noted in all three areas in the right leg, but the greatest proportional rise, 6.1°C. , occurred in the right foot. The next day there was a similar rise on the dorsal surface of the left foot. On the ninth day after operation the temperature of the thigh had returned to the preoperative level, while it was still elevated in the feet. The temperature of the mouth remained normal during the entire postoperative period.

CASE II.—The preoperative skin temperatures were higher in the right foot than in the right thigh. On the afternoon of operation a rise of 1.4°C. occurred in the right leg and a greater rise in the left foot. On the fourth day the temperature levels remained unchanged in the right leg, whereas there was some decrease in the left. Temperatures of the mouth were normal during the period of convalescence.

CASE III.—Sharp rises in temperature were noted in this patient. There were slight differences in the temperature of the thigh and feet before operation. On the day following operation an increase of 2.7° in the right leg and of 2° in the left was noted, whereas increases of 6.4° and 4° were obtained in the right and the left foot, respectively.

CASE IV.—The day following operation a temperature increase of 7.5° was noted in the left foot, and 3.6° in the outer aspect of the left thigh. Nineteen days after operation increases of 5.1° in the left foot and 2.6° in the right thigh were obtained.

CASE V.—Temperature increases of 2.5° occurred in the right foot the day following operation, while no change was demonstrated in the outer area of the thigh. Fifteen days later the right foot showed an increase of 1.2° , as compared with the preoperative temperature. There was no further change in the temperature of the thighs.

TABLE I.—SKIN TEMPERATURE DETERMINATIONS BEFORE AND AFTER ABDOMINAL SYMPATHETIC RAMISECTION AND GANGLIONECTOMY.

Case.	Date.	Age and sex.	Diagnosis.	Temperature.												Remarks.
				Mouth*	Right. †			Left. †								
					Thigh.		Foot.	Thigh.		Leg.	Foot.					
					Inner.	Outer.	Outer.	Palmar.	Inner.	Outer.	Outer.	Dorsal.	Palmar.			
1	1924	10 M.	Spastic paraplegia	32.6	31.6	35.5	Bilateral lumbar sympathetramisection and ganglionectomy, July 5.		
	7/4			99.0	38.1	37.7	36.1	37.0	36.6				
	7/5			98.6	35.5	38.3	36.6	36.6				
	7/6			98.6	36.2	35.1	34.2	36.9	36.1				
	7/9			98.4	37.2	37.2	36.1	36.1				
7/11	98.4	35.5	35.0	34.4	33.5	35.0						
7/14	98.0	35.3	33.3	35.0	34.4	33.5	35.0						
2	7/7	12 M.	Spastic paraplegia	33.7	34.7	35.0	34.8	34.8	Bilateral lumbar sympathetramisection and ganglionectomy, July 8.			
	7/8			98.4	33.8	36.4	35.0	37.1	38.4					
	7/10			99.0	36.1	35.1	36.4	35.0	35.3	36.6				
	7/11			99.2	36.4	37.4	36.1	34.0	36.6					
	7/12			98.6	36.1	35.7	37.2	36.0	34.0	36.6				
3	9/30	24 F.	Cerebral palsy.	32.5	31.6	33.8	34.1	34.1	Bilateral lumbar sympathetramisection and ganglionectomy, October 2.			
	10/3			37.0	35.2	38.1	36.1	36.1	38.1				
4	1925	28 F.	Spastic paraplegia	32.3	26.6	32.5	32.4	29.4	Bilateral lumbar sympathetramisection and ganglionectomy, February 26.			
	2/24			36.1	35.5	36.9					
	2/27			30.2	34.9	35.1	33.1	34.5					
	3/17							
5	2/16	51 M.	Spastic paraplegia	34.8	33.1	33.8	36.1	34.6	33.5	Bilateral lumbar sympathetramisection and ganglionectomy, February 17.			
	2/17			35.5	36.5	36.3	35.1	35.3				
	2/19						
	2/23			33.5	33.5	34.1				
	3/2			33.5	33.6	35.1				
	3/4			35.2	35.0	35.0	34.5	34.6	35.1					
	3/6			36.0	33.6	34.4				
	3/16			35.6	33.6	33.4				

* Fahrenheit.

† Centigrade.

TABLE II.—CALORIMETRIC STUDIES BEFORE AND AFTER ABDOMINAL SYMPATHETIC RAMISECTION AND GANGLIONECTOMY.

Case.	Date, 1924.	Sex and age.	Diagnosis.	Blood Pressure.			Temperature.			Foot.	Total calories for twenty minutes.	Square inches of surface area of foot.	Calories each minute for each square inch.	Remarks.
				Systolic.	Diastolic.	Pulse.	Mouth.*	Outdoor.†	Room.†					
1	7/4 7/4 7/5	10 M.	Spastic paraplegia	106	50	80	97.4	20.0	23.0	Right	660	70	0.47	Patient at rest. Bilateral lumbar sympathetic ramisection and ganglionectomy. Patient at rest.
				108	60	80	97.4	20.0	23.0	Left	1940	71	1.36	
				
3	7/23 7/23	98	58	96	98.8	30.0	29.5	Right	4600	..	3.28	Patient at rest. Bilateral lumbar sympathetic ramisection and ganglionectomy. Patient at rest.
				108	60	96	98.8	30.0	29.2	Left	3440	..	2.42	
				
3	9/30 9/30 10/2	24 F.	Spastic paraplegia	134	78	88	98.4	12.6	22.7	Right	600	73	0.41	Patient at rest. Bilateral lumbar sympathetic ramisection and ganglionectomy. After operation. Patient at rest.
				134	78	88	98.4	12.4	22.1	Left	480	70	0.34	
				
4	10/30 10/30	125	75	84	98.0	25.2	24.3	Right	5600	..	3.83	Patient at rest. Patient at rest. Bilateral lumbar sympathetic ramisection and ganglionectomy. Patient at rest.
				125	75	84	98.0	25.3	25.7	Left	5500	..	3.92	
				
4	2/24 2/25 3/19	28 F.	Spastic paraplegia	130	80	100	98.0	0.0	23.4	Right	560	69	0.40	Patient at rest. Patient at rest. Bilateral lumbar sympathetic ramisection and ganglionectomy. Patient at rest.
				128	80	85	97.8	9.3	18.2	Right	400	69	0.29	
				
5	3/19 3/24	112	86	84	98.0	4.2	22.1	Right	1480	69	1.07	Patient at rest. Patient at rest. Bilateral lumbar sympathetic ramisection and ganglionectomy. Patient at rest.
				97.8	5.0	22.2	Right	1520	69	1.10	
				
5	2/16 3/19	51 M.	Spastic paraplegia	130	80	80	98.0	0.0	22.8	Left	1840	77	1.19	Patient at rest. Patient at rest. Bilateral lumbar sympathetic ramisection and ganglionectomy. Patient at rest.
				
				102	58	98	98.0	4.2	22.3	Left	4640	77	3.01	

* Fahrenheit.

† Centigrade.

Studies of the heat conduction from the feet made with the foot calorimeter† further confirm the existence of the increased flow of blood following lumbar sympathetic ramisection and ganglionectomy. Determinations of the normal heat radiation under controlled conditions from the feet have shown a range from 0.5 to 3 small calories each minute for each square inch of surface area. Higher values in normals have been found during periods of excessively hot weather and represent the physiologic effects for increased radiation of heat from the skin. In hospital cases with control rest periods before tests and with standard room tempera-

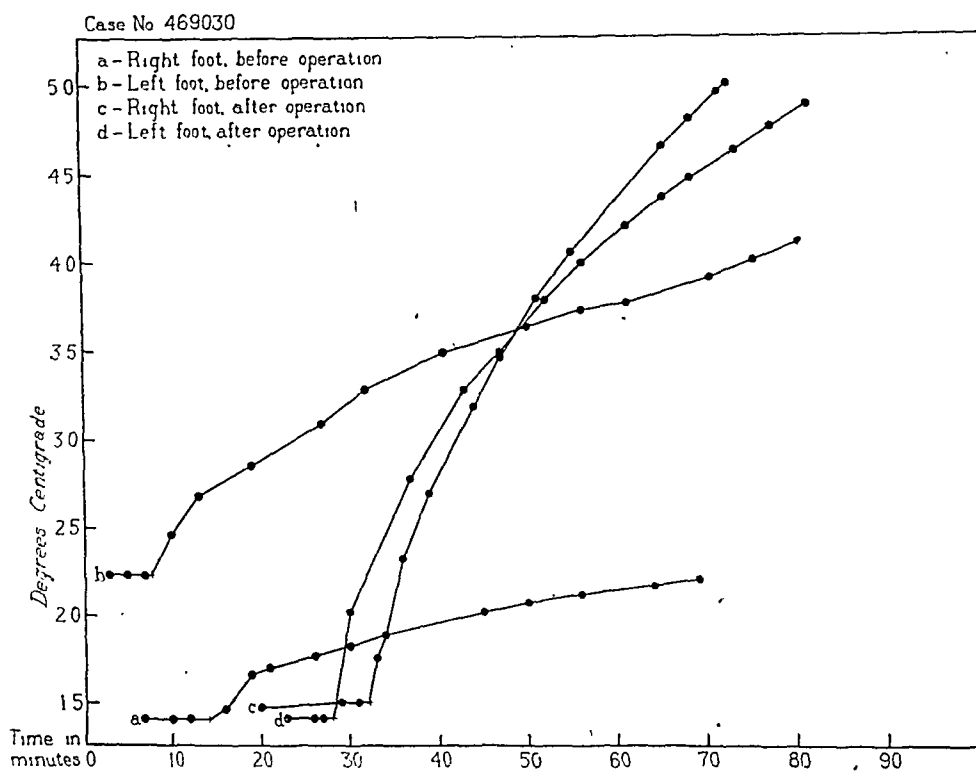


FIG. 1.—(Case I.) Heat curves, obtained by the Stewart-Kegerreis calorimeter, showing a marked increase in heat conduction from the feet, following lumbar sympathetic neurectomy.

ture a normal range of from 0.5 to 2 calories each minute for each square inch of surface area is found. Comparative readings under similar conditions check remarkably closely.

Preoperative values of 0.47 and 1.36 calories each minute for each square inch of surface area were noted in the right and the left foot, respectively (Fig. 1, Case I). Eighteen days after opera-

† This method determines the amount of heat given up to a known volume of water, in which the foot is placed. A special calorimeter is used. Corrections are made for heat loss of calorimeter and specific heat of metal container. A full report of the method, physical factors, and clinical studies is given in a group of papers by Sheard, Kegerreis and Brown.

tion the values were 3.28 and 2.42 calories. The total increase in calories amounted to 4000 and 1500 in the right and the left foot, respectively.

The preoperative values for heat production showed that the right foot in Case III gave up 600 calories in twenty minutes, or 0.41 calories each minute for each square inch of surface area, whereas the left foot gave up 480 calories, or 0.34 calories each minute for each square inch (Fig. 2). Twenty-eight days after operation the heat production had increased to 5600 and 5500 total calories for the right and left foot, respectively, or 3.83 and 3.92 calories each minute for each square inch of surface area.

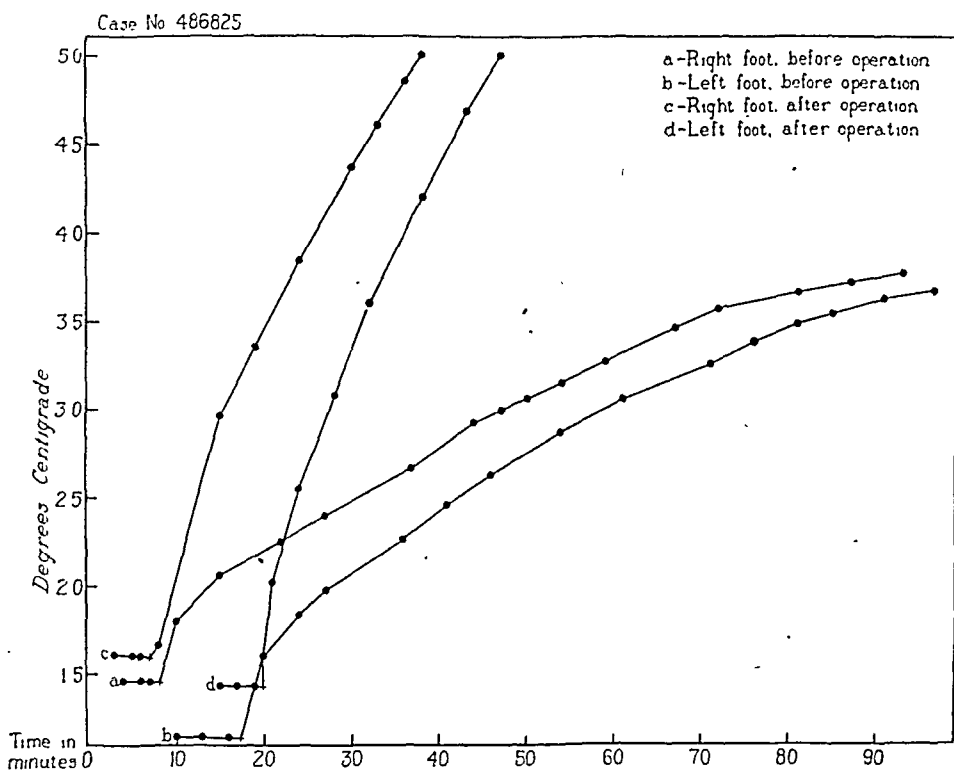


FIG. 2.—(Case III.) Increased heat production and heat conduction of the feet following lumbar sympathetic neurectomy, as determined by the foot calorimeter.

This change represents an increase of 900 per cent. These findings bore out the clinical observations, in which both objective and subjective findings attested to the hot dry condition of the skin.

Preoperative values for heat production in Case IV demonstrated that 0.29 and 0.4 calories were given up in the right foot each minute for each square inch of surface area. Thirty-two days after operation the heat production increased to 1.07 calories each minute for each square inch of surface area. There was a total increase of 1000 calories in the right and left feet following operation.

In Case V the preoperative values showed a heat production in the right foot of 1840 calories in twenty minutes, or 1.19 calories

each minute for each square inch of surface area. Thirty days after operation the total heat production had increased to 4640 calories during a twenty-minute period, or 3.01 calories each minute for each square inch of surface area. This represents an increase of 2800 calories, or 260 per cent.

Clinical Observations. The patient in Case IV was a young woman, aged twenty-eight years, who presented the clinical features of spastic paraplegia. Previous to operation the skin of the lower extremities showed a decreasing temperature toward the periphery. The feet were cool, pale and moderately moist. Following operation

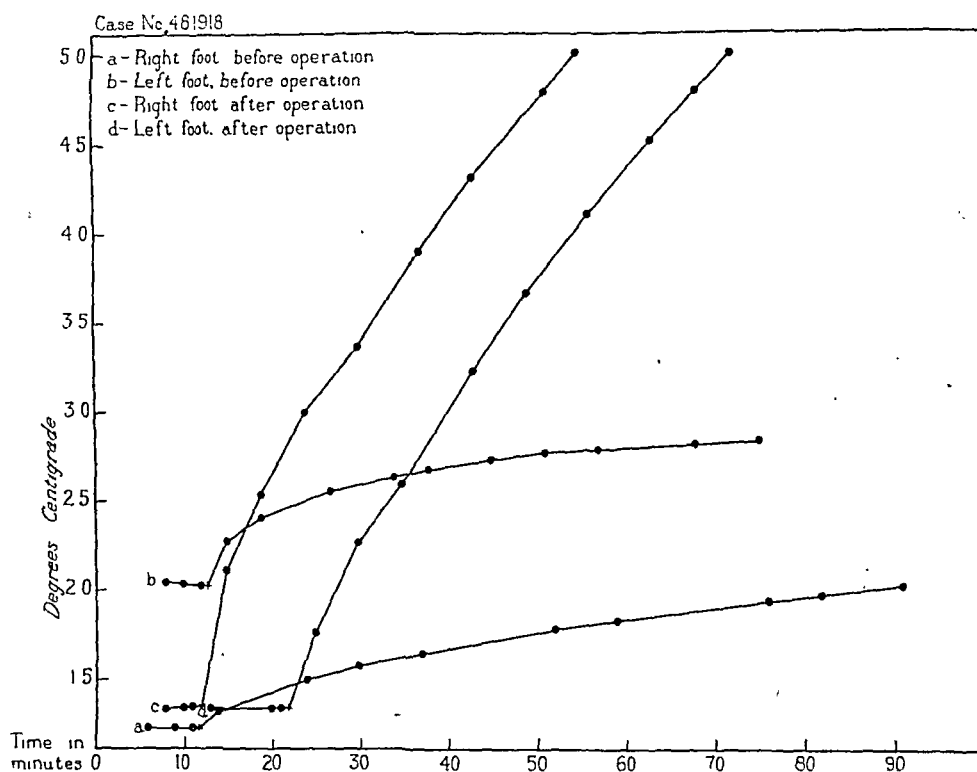


FIG. 3.—(Case IV.) Increased heat production and heat conduction of the feet following lumbar sympathetic neurectomy, as determined by the foot calorimeter.

and paralleling the calorimetric findings of elevated skin temperature the skin was very warm. A sharp temperature demarcation line could be established with the hand on the antero-lateral surface of the thigh 11 cm. below the anterior-superior spine. The feet were hot and dry. Twenty days after operation the feet were still hot to touch. There was no sweating below the line of demarcation. The skin of the dorsum of the feet had a slight ichthyotic appearance. Scaling was present. The lateral aspects of the feet were pink. The subjective symptoms were those of heat, although not to a degree to be troublesome. There were no demonstrable changes in the systemic blood pressure. A short, sharp attack of

cramps of the right quadriceps femoris muscles occurred forty days after operation.

In Case V the clinical manifestations of increased heat production were not as striking as in Case IV. The skin temperature of the feet was fairly high before operation; they were constantly warm and pink. Following operation no color changes were noted. Eighteen days after operation the skin was dry and scaly, especially of the palmar surfaces of the feet. The skin was hot to touch; the demarcation temperature line could not be established by touch. The subjective sensations were those of burning in the heels of both feet. No sweating could be demonstrated with Cobalt blue test papers.

Summary. Five cases of spastic paraplegia are reported in which bilateral lumbar sympathetic ramisection and ganglionectomy was performed. The second, third and fourth lumbar ganglia with the sympathetic trunk were removed and the rami divided. During the postoperative period marked increase in the skin temperature of the legs and feet was observed. Calorimetric studies with the foot calorimeter demonstrated marked increased heat production and heat radiation. There was complete absence of sweating in the legs in 2 cases. The vasomotor dilatation in the lower extremities, indicated by the calorimetric studies, was borne out by the clinical observations in respect to increased heat of the skin.

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DISEASE OF THE CORONARY ARTERIES.

CLINICAL AND PATHOLOGICAL FEATURES.

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AN accurate conception of a disease depends on our ability to correlate clinical manifestations with pathological changes. It is unfortunate that various types of cardiac diseases are named and classified by the clinician without regard for the underlying structural changes found in the heart at necropsy. Myocarditis, for

example, is a frequent clinical diagnosis, yet pathologically, true inflammation of the heart muscle is an extreme rarity. Cases, so classified clinically, often present at autopsy an enlarged heart, with normal valves, normal coronary arteries and practically normal heart muscle on microscopical section. The same clinical term is applied to cases which show at postmortem advanced coronary disease and fibrosis in the myocardium.

From a study of clinical data and necropsy findings, it has seemed possible to identify certain clinical features with certain definite pathological conditions in the heart. This report consists of such an analysis in cases showing coronary disease at autopsy.

In postmortem records coronary sclerosis appears as a rather frequent cause of death in adults. The exact frequency of this condition is difficult to estimate. Of 849 autopsies in 1923, from the records of the Department of Pathology of the University of Minnesota, there were 28 deaths attributed to coronary sclerosis. Of these 849 cases 339 were above the age of forty years. Of the 28 coronary cases 27 were above this age (96.4 per cent). The following table gives the incidence in the various decades above forty years.

TABLE I.—INCIDENCE OF CORONARY DISEASE ABOVE THE AGE OF FORTY YEARS.

Age, years.	Autopsies.	Coronary disease.	
		No.	Per cent.
40 to 49	90	6	6.6
50 to 59	94	6	6.4
60 to 69	105	10	9.5
70 to 79	42	5	7.0
80 to 90	8	0	0.0

During the same age periods there were 70 cases of malignancy of various types as compared with the 27 of coronary disease. Twelve of the coronary cases were from the coroner's service, and this would have a tendency to exaggerate the frequency to a certain extent, since the incidence of coronary deaths in coroner's autopsies is greater than that of the average postmortem material. Although this would reduce the incidence of coronary disease in the general population below the figures given, this analysis indicates that the condition stands out as one of the frequent causes of death in individuals above the age of forty years. In spite of its relative frequency and serious nature, however, there appears to be no generally accepted clinical picture of this disease.

Coronary Sclerosis and Angina Pectoris. The clinical syndrome, angina pectoris, was first described as a disease entity by Heberden, in 1768. Following this Jenner and later Parry ascribed this condition to disease of the coronary arteries. Throughout the last century there was a general tendency to consider coronary sclerosis

and angina pectoris as synonymous. Even in the earlier literature, however, there are many reports of exceptions to the association of angina pectoris and coronary disease. The literature on this subject has been very extensive, and in more recent years a number of theories have been advanced for the causation of angina. Disease of the aorta, myocardial exhaustion and dilatation, neuritis of the cardiac nerves and many others have been suggested as the underlying mechanism of this disease. Huchard¹ collected as many as eighty hypotheses for the basis of angina. Allbutt² vigorously denies any relationship between angina and coronary sclerosis, and insists that the seat of the disease is in the proximal portion of the aorta. His views have attracted considerable attention, and have received support from other observers. It is not our purpose to discuss the various theories of angina. An excellent review may be found in Allbutt's book. It is sufficient to say, however, that careful observers have noted (1) coronary sclerosis at autopsy, without any of the clinical manifestations of angina, and (2) normal coronaries in typical cases of angina pectoris of long standing. It may be safely concluded then that the symptom complex, angina pectoris, cannot be accepted as the constant clinical expression of coronary disease.

Modern Clinical Concepts of Coronary Disease. In the textbooks and systems of medicine in common use there is little or no attempt to consider coronary sclerosis as a disease entity. As a result of the work of Herrick³ in this country, the clinical manifestations of a sudden occlusion of a coronary branch have received considerable attention. Herrick has pointed out that death need not follow immediately on obstruction of a coronary artery. He has presented a clinical picture of this condition, and has described four types. Since Herrick first called attention to this disease, there have been a number of case reports of coronary thrombosis with fairly characteristic clinical pictures. As a result, coronary thrombosis holds a definite place as a disease entity in the majority of the more recent books in medicine. However, the clinical manifestations of the slower, progressive, obliterative changes in the coronary vessels have not been emphasized, and as a result there is a remarkable lack of uniformity in the manner in which this condition is considered in modern literature. With a few exceptions, there is no attempt made to discuss coronary sclerosis as an entity. Romberg⁴ and Hirschfelder,⁵ to be sure, devote portions of a chapter to a consideration of coronary sclerosis as a disease. Both emphasize cardiac pain and acute dyspnea as characteristic features. Paroxysms of rapid heart action are also described. Osler and McCrae⁶ mention coronary changes in the discussion of angina, but report several cases in which the coronary arteries were negative. MacKenzie⁷ makes no attempt to treat this pathological condition as a definite disease entity. He emphasizes the relation-

ship to angina, but coronary changes are also mentioned in a chapter on "The Senile Heart," which clinically presents different manifestations. In another publication, discussing heart pain,⁸ he states that in hearts showing degenerative arterial changes at autopsy, "Pain was the chief symptom in a few, while others suffered no pain." Allbutt believes that sudden closure of a coronary artery produces symptoms, usually severe, sudden and protracted precordial or epigastric pain with collapse. He apparently, however, does not consider sclerosis, without sudden occlusion, of any great clinical significance, as the following statement from his book indicates: "It is freely admitted that coronary disease may, and indeed for the most part does, pursue its silent way without anginous or other storms." Lambert⁹ does not believe that coronary sclerosis can be accepted as the anatomic basis of angina pectoris, and no attempt is made to discuss coronary disease as a clinical entity. Meakins¹⁰ feels that we are not justified in accepting angina pectoris as a disease, but merely as a symptom complex for "a definite pathology of the heart muscle or coronary arteries has not been found." Thus, he treats neither angina nor coronary sclerosis as a disease, but in a chapter on cardiac pain merely refers to coronary sclerosis as a possible cause of this symptom. This brief review demonstrates that there is little attempt in the current textbooks to consider coronary disease as a clinical entity, and indicates the uncertainty and lack of uniformity in the present conception of the clinical significance of coronary sclerosis.

The object of this paper is to construct a clinical picture of coronary sclerosis from the analysis of the clinical data of a series of fatal cases which came to necropsy. The material for study was obtained from the Department of Pathology of the University of Minnesota and comprises records of 113 cases. All those included showed severe coronary disease, with marked narrowing and partial obliteration of one or more large arteries, and usually definite fibrosis or softening of the heart muscle. No case is selected in which there is not a marked narrowing of the lumen or a thrombus; and the general necropsy findings were such that coronary sclerosis was considered as a chief cause of death. It appears from the analysis of the available data that certain clinical manifestations are quite constant for the group as a whole. In other respects, however, there are definite differences in the picture presented. Thus a simple uniform clinical picture cannot be drawn, and subgroups, each with its own characteristic features, may be recognized. Thus the clinical data may best be presented in the following manner: (1) General clinical features, and (2) subgroups.

General Clinical Features. *Age and Sex.* The average age at the time of death was fifty-nine and two-fifths years. The youngest was thirty-two and the oldest eighty-eight years. There were but 2 cases under forty years and 73, or 65 per cent of the entire group

were between the ages of fifty and seventy years. The distribution in the various decades is shown in Table II. As to sex distribution, there was a definite preponderance of males. Of the 113 cases, 97 were males and 16 females, giving a ratio of 6 to 1. A correction is necessary, however, as in the necropsy material of the Department of Pathology there are at least twice as many males as females. This reduces the ratio to approximately 3 males to 1 female.

TABLE II.—AGE AT THE TIME OF DEATH OF 113 CASES OF CORONARY DISEASE.

Age, years.	No. of cases.
30 to 39	2
40 to 49	17
50 to 59	28
60 to 69	45
70 to 79	15
80 to 89	3

Symptomatology. The outstanding clinical feature, which was quite constant for the group as a whole, was the tendency for the symptoms to occur in attacks, unlike other forms of cardiac disease which usually develop with gradual onset and increasing intensity. Attacks were present in 80 per cent, while in 20 per cent the symptoms were those of progressive cardiac failure, and acute paroxysms were not prominent. As a rule, the attacks consisted of pain, less often of acute respiratory distress.

Pain. The type of pain was quite characteristic, being described most frequently as a sense of pressure or fulness rather than as an acute sharp pain. The following are some of the expressions commonly used, "an uncomfortable heavy feeling," "a sense of oppression or fulness," "a feeling of tightness or constriction," and in a few severe instances, "an intense vicelike sensation." Radiation to the shoulders and arms was quite infrequent, being present in but 10 per cent of the cases. In 3 instances the pain was limited to the left shoulder and arm. The most frequent site of the sensation of pressure or fulness was in the chest, being either substernal or precordial. However, in 25 per cent the pain was localized in the epigastrium. Belching, nausea and vomiting was frequently associated both with the chest and the epigastric types of discomfort. The descriptions often closely simulated the symptoms associated with various gastrointestinal disturbances, and in some instances resembled the picture which may be presented by an acute abdominal lesion. This condition undoubtedly explains some of the negative laparotomies, and the majority of deaths due to "acute indigestion," which are met with in those of advanced years.

Attacks of Respiratory Distress. This was present in about 10 per cent of the entire series. These attacks usually occurred in

cases in which the ordinary effort dyspnea of cardiac failure was absent or present in a minor degree. This symptom was most frequently described as a feeling of suffocation, or as a choking sensation, and often occurred during the night. The circumstances under which the attacks of pain and respiratory distress were induced are of interest. Although more frequently brought on by exertion, very often the attacks occurred during low levels of activity or awakened the patient from sleep. In one instance a diagnosis of an unimportant functional condition had been made, as the substernal distress was relieved by exercise. In a short time death occurred during an attack and necropsy revealed a marked coronary sclerosis. Sudden death likewise was usually not associated with exertion. The majority of deaths occurred during periods of rest or slight degrees of activity.

Although attacks were a constant feature of 80 per cent of the group, in 20 per cent the symptoms were those of progressive cardiac failure uninterrupted by attacks. Two characteristic features, however, were apparent: (1) Death occurred in most instances before edema of any degree had developed, and (2) sudden death terminated the cardiac failure with a greater frequency than occurs in failure associated with other types of cardiac pathology.

Clinical Types. The data presented thus far has dealt with the clinical manifestations which are fairly constant for the group as a whole. Coronary sclerosis presents a clinical picture which is quite uniform in certain respects. However, there is a definite lack of uniformity in two important features: (1) As regards the size of the heart, and (2) as regards evidences of congestive failure; thus subgroups may be recognized.

Size of Heart. In the majority of instances there was some increase in the weight of the heart, involving chiefly the left ventricle. The weight of the heart varied from 293 gm. to 850 gm., with an average weight of 464.2 gm. A heart weight of 400 gm. may be regarded as representing the upper limit of normal, and hearts weighing more than 400 gm., if valvular disease and glomerular nephritis are excluded, are usually indicative of hypertension. Of the 113 cases there were 68, or 60.1 per cent, in which the heart weight was above 400 gm., and 45, or 39.9 per cent, with a heart weight of 400 gm. or less. As regards the size of the heart, then, coronary sclerosis may be divided into two types: (1) With a heart of normal size; (2) with an enlarged heart, usually indicating hypertension.

Congestive Failure. When the heart fails stasis of the circulation occurs, resulting in certain symptoms and signs. The chief symptoms and signs are dyspnea, cough, edema and enlargement of the liver. Pathologically, the intensity of the passive hyperemia in the liver is the most accurate index of the degree of congestive failure. Judged by clinical signs and passive congestion of the

liver as found at postmortem; congestive failure was present in 46 cases, or 40.6 per cent, and absent in 67, or 59.3 per cent. Congestive failure was definitely more frequent in the cases showing cardiac enlargement. In the group with hearts of normal size congestive signs appeared in but 3 cases, or 6.6 per cent, while in 43, or 63.2 per cent, of those with enlarged hearts evidence of congestive failure was present. Taking into consideration, then, the variations in size of the heart and evidence of congestive failure, four subgroups may be recognized: (1) Heart of normal size, congestive symptoms absent; (2) heart of normal size, congestive symptoms present; (3) heart enlarged, congestive symptoms absent; (4) heart enlarged, congestive symptoms present.

Discussion. An analysis of the clinical and pathological findings in 113 fatal cases of coronary sclerosis which came to necropsy reveals the following. A fairly uniform clinical picture may be recognized, characterized by attacks usually of pain, less often of acute respiratory distress. In about 20 per cent, however, attacks do not play a prominent part, and the clinical manifestations are those of progressive cardiac failure. The 113 cases may be separated by the clinical and necropsy findings into four groups, because of the variations found in the size of the heart and evidences of congestive failure.

Type I includes those with a heart of normal size and without evidence of cardiac failure. The typical case gives a history of attacks of pain, either chest or abdominal, or of paroxysms of dyspnea. The patient otherwise seems in good health and there is no need for any limitation of his activities, as congestive failure is absent. Examination will show that the heart is not enlarged and usually no increase in blood pressure. This group presents considerable difficulty in diagnosis, as aside from the history of attacks, which may be very atypical, there are no symptoms or objective signs which indicate that there is either anatomical or functional damage to the heart. As a matter of fact, several cases had undergone a physical examination, and had been pronounced normal, and in a few instances an insurance examination had been successfully passed shortly before death. Of the 113 cases 37.2 per cent fall into this group.

In Type II are included those with hearts of normal size and with congestive symptoms present. This group exhibits a very different clinical picture, which is essentially that of cardiac decompensation. The patient is restricted in his activities because of shortness of breath on exertion, and edema may be present. Attacks of pain or acute respiratory distress may or may not be associated. There is little difficulty in recognizing that cardiac pathology is present, and coronary disease should be suspected as practically all other forms of cardiac pathology resulting in congestive failure are accompanied by enlargement of the heart, which is absent in this group.

Type III consists of those with cardiac enlargement in which the manifestations of congestive failure are absent. The picture is that of an individual who requires no restriction of activities and who is apparently in good health except for the occurrence of attacks of pain or acute respiratory distress. The heart is enlarged and the blood pressure is usually increased. This group is similar to Type I, but may be differentiated by the presence of cardiac enlargement and hypertension. This type includes 22.6 per cent of the entire series.

In Type IV are included the cases with cardiac enlargement and evidences of heart failure. The clinical picture is essentially that of cardiac decompensation. In most instances there is a history of attacks of pain or acute dyspnea, either preceding or associated with the symptoms of congestive failure, while in others attacks are entirely absent. Dyspnea and orthopnea are the outstanding symptoms. Edema is usually not marked or may be absent, and sudden death frequently terminates the cardiac failure. As to the recognition of this type, the evidence of reduction in functional capacity points at once to the heart as the seat of the pathology. As to the type of anatomical change, coronary sclerosis should be suspected when, in addition to the symptoms of congestive failure, there is also a history of attacks of pain or acute respiratory distress. Aside from the attacks, certain features are quite characteristic but not entirely diagnostic of this group. They are the following: (1) A history of congestive failure of comparatively short duration and rapidly progressive; (2) absence of marked edema; (3) tendency to sudden death; (4) a fairly characteristic electrocardiograph, with an abnormal form of the ventricular complex. Table III summarizes the essential features of the four types.

TABLE III.—CLINICAL TYPES OF CORONARY SCLEROSIS.

Clinical features.	No. of cases.
1. Heart not enlarged, congestive failure absent; symptoms of cardiac insufficiency absent; heart normal in size; blood pressure normal	42 or 37.2 per cent
2. Heart not enlarged, congestive failure present; symptoms of cardiac insufficiency present; heart normal in size; blood pressure normal	3 or 2.6 per cent
3. Cardiac enlargement, congestive failure absent; symptoms of cardiac insufficiency absent; heart enlarged; blood pressure increased	25 or 22.6 per cent
4. Cardiac enlargement, congestive failure present; symptoms of cardiac insufficiency present; heart enlarged; blood pressure usually increased	43 or 39.0 per cent

Illustrative Cases. TYPE I.—A male, aged fifty-four years, entered the hospital with the following history: He was in his usual health at the time of the onset of the present illness. While sitting in a chair he was seized with a severe pain in the abdomen. He fell

from the chair, and continued to complain of the pain. On examination the patient was practically comatose, there was a diffuse cyanosis of the skin, the heart was not enlarged and the tones were very weak. The systolic blood pressure was 50. There was tenderness in the upper abdomen and rigidity of the muscles. He was sent to the surgical division with a diagnosis of perforated gastric ulcer. On later examination the abdominal rigidity disappeared, but there was definite tenderness on pressure. The cyanosis increased and the patient died two and a half hours after admission.

At autopsy edema was absent. The heart weighed 325 gm. In the descending branch of the left coronary artery about 2 cm. from the opening there was a heavy calcareous intimal thickening, extending for a distance of about 2 cm. The lumen here was partially occluded. The entire length of this branch showed marked sclerosis. The other branches of the coronaries were slightly sclerotic but entirely patent. The root of the aorta was smooth. *The liver showed no evidence of congestion.* Other pathological findings were negative.

TYPE II.—A male, aged forty-six years, was admitted to the hospital with the following history. Five years ago he began to have attacks of precordial pain, and he also noted slight shortness of breath on exertion. Ten days ago he noticed swelling of the ankles, and his dyspnea became more marked. After four weeks' rest with improvement he was discharged from the hospital. He was readmitted two weeks later with similar complaints and his edema more intense. He was discharged from the hospital a month later, after some improvement. Nine days after discharge he was found dead in his room. A physical examination while in the hospital showed the following: Considerable edema; the heart was not enlarged and there was a blowing systolic murmur over the apex which was not constant. The blood pressure was: systolic, 108; diastolic, 60.

The autopsy findings were as follows: The heart weighed 395 gm. The ventricles were dilated, and both coronary arteries showed marked sclerosis and calcification. The myocardium on section showed multiple small whitish areas of fibrosis. The root of the aorta showed several yellowish calcified plaques, some of which were as much as 1 cm. in diameter.

TYPE III.—A male, aged sixty-one years, presented the following history: His past health was good. The present illness began seven years ago with a sudden attack of pain over the heart. This was attended with slight belching which brought some relief. During the past two years attacks of precordial pain had been very frequent. These usually occurred after meals or upon exertion.

The condition was more severe when he was constipated. He has never had any edema. On examination his complexion was pasty. A marked pyorrhea was present. The cardiac apex was displaced to the left; the tones were regular but distant. The lungs showed no evidence of congestion. The urine and blood were negative. Roentgen-ray examination showed the heart enlarged to the left. The patient died suddenly in an attack.

At autopsy the body was well developed and nourished. Edema and cyanosis were absent. The heart was markedly enlarged, weighing 575 gm. The valves were normal. There was a large scar on the inferior surface of the left ventricle and another on the anterior surface of the right chamber. The right coronary artery was completely obliterated in the first 2 cm. of its extent. There was also a marked narrowing of the left coronary. One of the large muscular branches, descending on the inferior surface of the left ventricle, was almost completely closed. The root of the aorta showed numerous raised yellow patches on the intima, but no calcification. *The liver was not enlarged and showed no congestion.* On microscopical examination there was extensive fibrosis in the heart. The liver was negative and the kidney showed sclerosis of a few small arterioles, which is a good evidence of hypertension.

TYPE IV.—A male, aged fifty-two years, entered the hospital with the following history. One year ago he began to suffer attacks of pain in the upper abdomen, radiating to the precordium. These often continued for as long as three hours. About six months after the onset of these symptoms he had an attack of influenza, following which his distress became more marked. He also developed shortness of breath on slight exertion and edema of the ankles. At the time of entrance to the hospital he was unable to walk 50 yards without severe distress in the upper abdomen, and marked dyspnea. On examination the patient showed all the signs of advanced cardiac failure. Cyanosis of the fingers and lips was present. There was slight edema of the chest wall and moderate edema of the extremities. The heart was enlarged, the left border extending 3 cm. outside of the nipple line. The arterial pressure was: systolic, 150; diastolic, 90. The liver was enlarged. During his stay in the hospital the patient had no attacks of pain. He died suddenly while in bed.

At autopsy the heart was definitely enlarged, weighing 550 gm. The chambers were dilated. At the apex of the left ventricle there was an area of thinning and marked connective-tissue replacement. A soft mural thrombus was attached to the endocardium covering this fibrous area. The right coronary artery showed marked calcification and narrowing. The left coronary was also severely involved and a recent thrombus was present in one of the branches. The root of the aorta presented the usual amount of senile sclerosis.

The pleural cavities showed fluid on both sides and a moderate amount was also present in the peritoneal cavity. There was a definite passive congestion of the liver and spleen.

These 4 cases illustrate the difference in the clinical picture presented. In Cases I and III the outstanding feature is the occurrence of an acute attack of pain, in one instance in the abdomen, in the other in the chest, in an individual otherwise apparently healthy. There was no congestion of the liver in either case, which further indicates that the symptoms of congestive failure which produce a restriction of activities were absent, such as effort dyspnea and edema. Cases II and IV, although attacks of pain occurred in both instances, are essentially pictures of cardiac decompensation. In Case II the heart and blood pressure are within normal limits, while in Case IV there is cardiac enlargement and the blood pressure is increased. Although coronary sclerosis is the underlying pathological change, it is apparent that each of the cases shows a somewhat different clinical picture.

Coronary Thrombosis. Of the 113 cases of coronary disease studied there was a thrombus occluding a large coronary branch in 24, or 21.2 per cent. An advanced degree of sclerosis was present in all instances. Those showing a thrombus were distributed in the four subgroups as follows:

TABLE IV.—DISTRIBUTION OF CORONARY THROMBOSIS IN FOUR SUBGROUPS.

Type.	No. of cases.
I	12
II	0
III	7
IV	5

In contrast to the uncertain and indefinite conception of the clinical manifestations of coronary sclerosis, sudden occlusion of a coronary vessel is generally regarded as possessing a definite clinical picture. Leyden¹¹ states that coronary occlusion is not necessarily accompanied by pain, but that dyspnea and other evidences of cardiac failure are fairly constant findings. Obrastzow and Strashesko¹² describe attacks of precordial pain associated with this condition, but point out that the principal signs are diminishing heart sounds and symptoms of heart failure. Allbutt,² who definitely disregards coronary sclerosis as a clinical entity, believes that coronary thrombosis has certain characteristic clinical manifestations which differ, however, from ordinary angina. The pain is often more continuous than that of ordinary angina, but the feature which he believes clearly separates coronary thrombosis from ordinary angina is the evidence of myocardial failure, such as rapid irregular pulse, weakening heart tones, dyspnea and cyanosis. Herrick,³ in this country, has made a careful study of the sub-

ject, and divides the clinical manifestations into 4 types. His first type is characterized by sudden death. In Type II there is a sudden attack of cardiac pain, and death is deferred for several minutes to hours. In Type III the symptoms are severe and prolonged and death may not occur for days or weeks. Type IV is a hypothetical group in which the symptoms are slight attacks of pain, supposedly due to obstruction of small coronary branches. Herrick has described his third type at considerable length. The patient usually has suffered previous paroxysms of cardiac pain, but the present attack is described as the most severe and prolonged. The pain may be substernal, precordial or epigastric. Vomiting may be present. The patient is usually in collapse and the pulse rapid, small and occasionally irregular. The blood pressure is low in contrast to the usual attacks of angina. If the patient lives for a few days or weeks the signs of cardiac failure, such as dyspnea, cough and edema, follow. Twenty-three of the 24 cases of thrombosis in this series present clinical manifestations which can be grouped fairly well according to Herrick's classification and are distributed as follows: Type I, 10; Type II, 3; Type III, 10. Type IV was not taken into consideration, as all of the cases of thrombosis selected from the series were occlusions of large branches.

In the analysis of the clinical manifestations of the entire group of coronary disease, it seemed that certain of the features, described as characteristic for coronary thrombosis, occurred also in many instances where a thrombus was absent. To ascertain more definitely whether this were true, a group of 40 unselected cases of coronary sclerosis, without a thrombus, was carefully analyzed following Herrick's classification. Sudden death occurred in 20 cases corresponding to Herrick's Type I. In 13 an acute attack of pain followed shortly by death, as in Type II. In 7 instances the history was that of a prolonged attack with incomplete recovery which the patient survived for varying lengths of time, a picture which is similar to that described by Herrick as Type III. The following is an illustrative case:

The patient was a male, aged fifty-one years. His past health was good, with the exception that he had noticed some shortness of breath and slight precordial distress on exertion during the past two months. The onset of the present illness was acute, starting after his evening meal with a sharp epigastric pain and vomiting. The pain persisted through the night. On examination the following morning pain was still present; pulse was rapid, rate 130, but regular; the blood pressure was: systolic, 100; diastolic, 70. There was some tenderness over the gall bladder. The patient was seen again two days later. At this time pain was absent, but he complained of marked weakness. His heart was negative on examination except for a tachycardia. He made an attempt to be up and around, but was unable to and was forced to rest in bed. Twelve

days following the initial attack, while in bed listening to the reading of a letter, he suddenly gasped and died. The autopsy revealed the following. There was a slight edema of the ankles. The heart was normal in size, weighing 300 gm. The coronary arteries showed extensive sclerosis, being almost closed at several points, especially in the anterior descending branch of the left coronary. The right coronary was definitely involved but to a lesser degree. There was considerable fibrosis of the muscle, a portion of the anterior wall of the left ventricle being completely replaced by scar tissue. There was a marked narrowing of the vessel to this area but no thrombus. The liver weighed 1850 gm., and the centers of the lobules were prominent, indicating congestion. Interesting points in this case are the prolonged character of the pain, the incomplete recovery and the onset of signs of cardiac failure. The entire picture follows closely that which Herrick describes for Type III of coronary thrombosis. However, although an extensive sclerosis was present, there was no evidence of a thrombus. It seems justifiable to conclude from this analysis that coronary disease shows a similar clinical picture irrespective of whether a thrombus is present or not. A prolonged attack, consisting of an initial shock which the patient survives, is more frequent with a thrombus. Such a picture does occur, however, in coronary sclerosis without thrombosis. There does not seem, therefore, to be any justification for drawing any sharp distinction between these conditions. Since coronary thrombosis is constantly associated with sclerosis of the vessels, it is most reasonable to regard a thrombus not as an entity, but merely as one of the end results of coronary disease, occurring in approximately 20 per cent of the cases.

Pathological Features. Although our chief attention in this study was focused on the construction of a clinical picture, certain of the pathological findings which might have clinical significance were also noted. The data concerning the anatomical changes in the coronary arteries, the heart and the aorta were analyzed.

CORONARY ARTERIES. The changes in the coronary arteries were of a marked degree, as this was the chief criterion for the selection of the cases. There was definite thickening of the walls with areas of marked narrowing of the lumen, and in many instances there was complete obliteration of portions of the vessels. Calcification of the walls was infrequent. Although in general, sclerosis occurred in both coronaries, there was a definite tendency for the changes to be much more extensive in the left branch. In 20 of the 113 cases, or 18 per cent, however, the degree of involvement in the right coronary was as great as that in the left, or even more marked. In the left coronary artery the branch that was most frequently and extensively involved was the anterior descending ramus, and in a number this was the only branch to show a marked sclerosis.

THROMBOSIS. A thrombus occluding one of the larger branches was present in 24 cases, or 21.2 per cent. It occurred in 22 per cent of the 45 hearts under 400 gm., and in 20.6 per cent of the 68 larger hearts. It is of interest to note that there was a marked difference in the degree of sclerosis of the coronary vessels as compared with the other arteries of the body. In many instances in which the coronary showed extensive change the other arteries, including the aorta and brain vessels, were only slightly involved. This is of some practical importance, as it indicates that one cannot judge the condition of the coronary arteries from the appearance of the vessels accessible for examination, such as the peripheral arteries or retinal vessels. In 4 cases there was a history of diabetes and a marked sclerotic change in the pancreatic artery, with degeneration of pancreatic tissue. In 2 additional cases diabetes was present, but no note was made of the condition of the pancreatic artery. Since these observations were made several clinical cases of diabetes associated with coronary disease have been seen, and it is possible that in a certain percentage a degree of pancreatic artery sclerosis sufficient to produce diabetes may occur with coronary disease.

TABLE V.—DISTRIBUTION OF HEART WEIGHT.

Heart, weight, gm.	No. of cases
200 to 299	1
300 to 399	30
400 to 499	37
500 to 599	30
600 to 699	5
700 to 799	2
800 to 899	2

MYOCARDIUM. As has already been mentioned, the heart showed some hypertrophy in a large percentage of the cases. Although there was some involvement of the right side, the preponderance of hypertrophy was in the left ventricle. In Table V the distribution of the heart weights of the entire group is given. In addition to the presence of hypertrophy, a degenerative change in the heart muscle was practically a constant finding in all of the 113 cases. This is in definite contrast to the hypertension heart without coronary sclerosis, in which such changes in the heart muscle occur only in a minimal degree. The myocardial involvement consisted chiefly of a fibrosis, which varied from a slight degree to an extensive connective tissue change. This was usually more marked in certain portions of the heart, but occasionally occurred as a diffuse fibrous infiltration. As with the coronary arteries, fibrosis was most marked in the left ventricle. The most frequent site of thinning and connective-tissue replacement was in the apex of the left ventricle. In many cases the entire thickness of portions of the ventricular wall was replaced by connective tissue. There

was no relation between the degree of fibrosis and the size of the heart. Equally extensive changes were found in hearts under 400 gm. as in those above this weight. In 16 cases, or 14.1 per cent, necrosis and softening was found in one or more areas. In 5 of these there was a rupture of the ventricular wall and in 1 a saccular dilatation in the left ventricle. The constant presence of myocardial change with coronary disease has been well shown by Clawson,¹³ in a recent report. He made a careful detailed gross and microscopical study of the myocardium in 102 cases of noninfectious myocardial failure. His conclusions were that myocardial fibrosis is usually due to coronary disease and that there is a close correspondence between the location and extent of fibrosis and the distribution and degree of coronary sclerosis.

AORTA. A change of some degree was present in practically all the cases. This consisted chiefly of the presence of raised intimal patches and calcification. The involvement in the aorta, with a few exceptions however, did not seem to be any more marked than normally occurs at this age period, and could not be considered of any clinical importance. In 7 cases there was evidence of definite pathology in the aorta; 4 showed dilatation of the wall and 1 aorta had a definite thinning of the wall but no dilatation. In 2 other cases there were patches with linear depressions present, and involvement of the mouths of the coronary arteries. Lues was suspected in each of these 7 cases. Thus definite pathology occurred in the aorta in but 7 of the 113 hearts, or 6.2 per cent. This is of considerable interest in relation to Allbutt's views, for in this series the anginal type of syndrome was the outstanding clinical feature, and yet aortic pathology of any significance was present in but a small percentage. One must conclude therefore that, although lesions in the aorta may give rise to anginal symptoms, this is not the only mechanism, since coronary disease in itself is a frequent factor in the production of cardiac pain.

THE ELECTROCARDIOGRAPH. The constant finding of myocardial changes with coronary sclerosis would lead one to expect alterations in the form of the electrocardiogram. Unfortunately, there were electrocardiographical records in but 5 cases. In 4 these were definitely abnormal. In 1 the tracing was that of a bundle-branch block. In the remaining 3 there were alterations in the form of a *T* wave. This is too small a series from which to draw any conclusions. However, in a group of approximately 40 cases, which clinically would fall definitely into one or the other of the types of coronary disease discussed, electrocardiographical abnormalities occurred in about 50 per cent. This will be considered in detail in a later report.

Summary. Since there is no generally accepted conception of the clinical significance of coronary sclerosis, an attempt was made to construct a clinical picture by an analysis of a series of fatal

cases which came to necropsy. The following points are brought out by this study:

1. Coronary sclerosis is most common in males and in the age period between fifty and seventy years.

2. The outstanding clinical feature is the presence of attacks, usually of pain, less frequently of acute respiratory distress. The pain is most often in the chest, but abdominal attacks are not uncommon.

3. These attacks occur with either of the following combinations:

(a) Normal sized heart, with no evidence of cardiac failure, 37.2 per cent.

(b) Normal sized heart, cardiac failure present, 2.6 per cent.

(c) Cardiac enlargement, congestive failure absent, 22.6 per cent.

(d) Cardiac enlargement, congestive failure present, 38 per cent.

4. The clinical features of coronary thrombosis are essentially similar to those of coronary sclerosis; thrombosis, therefore, should not be considered as a clinical entity but merely as a complication of coronary sclerosis.

5. The outstanding pathological features are the following: Changes in the coronary arteries are most marked in the left branch. In addition to coronary sclerosis, thrombosis occurs in approximately one-fifth of the cases. Myocardial involvement paralleling the degree of coronary sclerosis is a constant finding. Lesions in the aorta of any significance are present in but a small percentage.

NOTE.—I am indebted to Dr. E. T. Bell, head of the Department of Pathology, for the opportunity of studying these cases.

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RECTAL ETHER ANALGESIA IN CHILDBIRTH.*

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LESSENING the suffering of the woman in childbirth by means of morphin and magnesium sulphate hypodermically, followed by colonic instillation of ether in oil, was first conceived by Dr. J. T. Gwathmey, and put in practice by him at the New York Lying-In Hospital in February, 1923. It proved to be an effective and harmless way of utilizing these familiar and inexpensive drugs, and one that could be employed by any physician without special training. With the encouragement and perseverance of Dr. A. B. Davis and the attending staff, a procedure gradually has been evolved which we are now pleased to call our standard method of obstetrical analgesia. It is this method, still unquestionably open to improvement and to be adapted somewhat to the individual needs of the patient, that I wish to present.

We have conducted the experiments with an open mind, freely criticizing among ourselves defects in technic or disadvantages that any of us could possibly note, being ready at all times to abandon it if it proved dangerous, beginning with small doses and trying various combinations until we have arrived at the routine about to be described. The procedure consists essentially in a deep intramuscular injection of one dose of morphin with magnesium sulphate in solution to prolong its action, repeating the magnesium sulphate alone, and following it in from one to two hours with a rectal instillation of ether in olive oil which is retained, employing about half the quantity of ether necessary for surgical anesthesia by rectum. The effect is a seminarcois and amnesia, with great relief of pain, similar in appearance to the condition in "twilight sleep," and, when not used too early, without inhibiting the progress of labor, even in the perineal stage.

In the seminarcois and amnesia produced by the use of scopolamin and narcophin, some years ago, we found we had a method that could be employed over a sufficient length of time to relieve the nervous exhaustion of labor without largely inhibiting its efficiency. The disadvantages of twilight sleep were two: A lesser disadvantage was the lack of good bearing-down pains in the perineal stage, and the increased necessity for forceps; the second disadvantage, and the greater one, was its effect upon the respiration of the child at birth. In a report published some ten years ago from the Lying-In Hospital in over 250 cases we had but 2 stillbirths, and these seemed to have sufficient obstetrical cause apart from the narcotics employed. But I think all of us now agree that

* Read before the Philadelphia County Medical Society, March 11, 1925.

with scopolamin and morphin pushed to the degree required for perfect amnesia, while we had no more stillbirths we had too many alarms, too many babies that when born gave a cough or a gasp and then lay there in an apneic state that was very disturbing. They opened their eyes, stretched their arms and legs, but did not breathe for a considerable number of minutes. These are probably the chief reasons why we have all abandoned the typical twilight sleep. However, many men throughout the country are still giving, with more or less satisfaction, a single dose of morphin and scopolamin during the first stage of labor.

With the rectal ether analgesia we do not pretend nor promise a painless labor, but great relief of suffering is experienced in a very large majority of the cases, and the patients sometimes claim marvelous results. The details of rectal analgesia are as follows:

The drugs required: 1. Magnesium sulphate with morphin. This can be procured in ampoules containing 2 cc of a 50 per cent solution of magnesium sulphate with $\frac{1}{6}$ or $\frac{1}{4}$ gr. of morphin sulphate.

2. Magnesium sulphate alone. Ampoules containing 2 cc of a 50 per cent solution are to be had.

3. The retention enema. This can readily be prepared by any druggist. It consists of:

Quinin alkaloid	gr. xx
Alcohol	℥xl
Ether	℥iiss
Olive oil	q. s. ad ℥iv

If the quinin alkaloid is not obtainable, the following formula may be used with equal satisfaction:

• Quinin hydrobromate	gr xx
Alcohol	℥iii
Ether	℥iiss
Olive oil	q. s. ad f℥iv

This, if well bottled and corked, may be kept at room temperature and is undoubtedly stable for at least a month. Should it be necessary, as it occasionally is, to repeat the instillation of the retention enema, subsequent ones should contain only 10 gr. of quinin, the other ingredients remaining the same.

4. A bottle containing 2 ounces of olive oil.

The necessary apparatus is simple. Besides a 5-cc glass hypodermic syringe with a long needle for intramuscular use, it consists of a 5-ounce funnel attached to 20 inches of rubber tubing which is in turn connected by means of a 4-inch glass connecting tip to a red rubber catheter, size 20 or 22 French. A rectal tube is too large and allows the instillation to run in too rapidly. The glass connecting tip enables the observer to note when the last of the fluid leaves the funnel.

The treatment should not be started until the woman is in active

labor. The pains should be at least at five-minute intervals and lasting at least forty seconds. The length of the contractions are best judged by placing the hand on the abdomen and timing them with the watch, as the outcry of the woman is often a poor index of the strength of the pain. Waiting for the labor to be well established thus at once eliminates cases of so-called primary inertia from treatment. In a primipara it is best to wait until the cervix is fairly well effaced and dilated to a diameter of at least two finger tips; in a multipara it can be started before this degree of cervical dilatation is reached if the pains are of the proper length and interval as described. At this time a cleansing soapsuds enema is given and this is followed with the primary deep intramuscular injection of $\frac{1}{6}$ or $\frac{1}{4}$ grain of morphin and 2 cc of 50 per cent solution of magnesium sulphate given into the gluteal region. Judgment must be used as to the soapsuds enema, as it may not be required if the customary soapsuds enema at the onset of labor has been recently given. The rectum must be both empty and quiescent to properly retain the instillation of ether in oil that is to follow the primary morphin and magnesium sulphate intramuscular injection. Experience shows $\frac{1}{4}$ gr. of morphin usually to be the proper dose, but in a small woman $\frac{1}{6}$ gr. will be sufficient. Labor should be well under way so that the morphin will not stop the uterine contractions altogether. Give the injection during an active pain when the discomfort will be least noticed. Tell the patient the object is to relieve her pain, but do not promise her a painless labor.

After this primary intramuscular injection of morphin and magnesium sulphate the patient is to be kept quiet, oiled cotton placed in the ears and the room darkened. These attentions are reminiscent of the scopolamin amnesia suggestions, but they are of undoubted value in the proper induction of any seminarcosis.

One-half hour after the primary morphin and magnesium sulphate injection we give a second intramuscular injection, consisting of 2 cc of 50 per cent solution of magnesium sulphate alone. This is given no matter whether the effect of the primary injection is sedative or not, and tends to prolong the action of the morphin.

We now come to the manner of giving and the time of the rectal instillation. It again must not be used too soon. If the effect of the morphin and magnesium sulphate is sedative withhold the instillation until the effect of the former is almost worn off. It is easier to give when the patient is still somewhat under the effect of the morphin; however, three- to five-minute intervals between uterine contractions should be present. For the beginner it is better to let the morphin and magnesium sulphate wear off entirely and to withhold the instillation until the patient is again complaining and the pains, at three- to five-minute intervals, are good and strong. If there is no relief from the morphin and magnesium

sulphate within one-half hour after the second injection, which consisted of 2 cc of 50 per cent magnesium sulphate alone, proceed with the ether instillation. The ether instillation thus rarely should be given within an hour after the first injection of morphin and magnesium sulphate. It may be from one to three hours before it is needed, depending on the patient's distress. The ideal time in a primipara is at about three finger tips' dilatation of the cervix.

It is given as follows: The contents of the bottle containing the ether mixture and the bottle containing 2 ounces of plain olive oil are warmed by letting them stand for a few minutes in warm water, first loosening or removing the corks. The patient is then placed on her left side and vaseline is liberally applied around the anus so that the ether mixture if expelled will not irritate. State to the patient just before beginning the instillation that its object is to relieve her pain and thus secure her coöperation. Tell her that during the instillation she is not to press down during pains, but to breathe deeply with her mouth open, and at all times to "draw up" with her sphincter as if she were trying to avoid expelling gas. This will tend to induce reverse peristalsis and permit the fluid to run in more readily. Pour into the funnel 1 ounce of the warm plain olive oil. Just as the oil runs out of the catheter pinch the latter near the glass connecting tip with an artery clamp. In this way all the air will be expelled from the tubing. Some of the 1 ounce of oil should still remain in the funnel. The catheter is now introduced into the rectum for about 4 inches. If the fetal head is well down in the pelvis the gloved finger must be inserted into the rectum along with the catheter to insure its passage past the head. A little of the warm ether mixture is added to the oil in the funnel, the clamp released and the contents of the funnel slowly permitted to run into the rectum. The remainder of the ether mixture is gradually added, at no time permitting the funnel to become entirely empty. Just as the last of the ether mixture is about to leave the funnel add the remaining ounce of the warm plain olive oil. Allow this to start running into the rectum and clamp the tube. It is important in order to avoid the expulsive desire that we prevent the entrance of any air bubbles into the rectum. Now make pressure on the anus with a towel during two or three contractions, leaving the pinched catheter in place meanwhile, then gently withdraw the catheter. Should a uterine contraction intervene during the instillation simply make pressure against the anus with a folded towel and let the funnel act as the escape reservoir. Continue to make pressure over the anus during three or four contractions after the catheter is out. All these details are important and the successful retention of the instillation largely depends on the meticulous care with which it is given.

A third intramuscular injection of 2 cc. of 50 per cent solution

magnesium sulphate alone is then given immediately to prolong the action of the ether. The patient may now turn upon her back or assume whatever position is most agreeable to her. The same quiet is maintained as before. Do not make a vaginal or rectal examination too soon after the instillation or the instillation will be expelled. Do not be misled by the quiet behavior of the patient into thinking she is having very slight contractions or none at all. Within fifteen or twenty minutes you can smell ether on her breath, she becomes flushed and occasionally has a little of the excitability of the first stage of ether anesthesia, but never to the extent of requiring restraint.

The patient is drowsy and sleeps lightly between the pains, but consciousness is not entirely lost. She responds somewhat tardily to questions and usually obeys commands as to change in posture. When a uterine contraction occurs she manifests her suffering to a greater or less degree and again dozes. Occasionally the casual observer would have the impression that there was very little amelioration of the pain, the patient complaining and restless during the contractions, and yet afterward we find the amnesia secured to have been as definite as that after scopolamin. Frequently the patient confesses of her own volition that she remembered very little after the rectal instillation was given.

The obstetrical side of the case and the progress of labor must be closely watched, for the presenting part frequently is bulging the perineum without any apparent increase in effort on the part of the patient. Functional abnormalities must be discovered and corrected as they arise, and the mechanism of labor followed and managed as thoroughly as though no analgesia were being employed.

When the effect of the first ether instillation has worn off, that is, when the patient again complains of pain, which is usually in from two to three hours, a second, or even a third, rectal instillation may be given at intervals of three hours or more. The first instillation is given containing 20 gr. of quinin alkaloid; in subsequent instillations only 10 gr. Each subsequent instillation is accompanied with one intramuscular injection of 2 cc of 50 per cent magnesium sulphate. Contrary to some authorities we are convinced that the quinin is absorbed by the rectum, as evidenced by the occasional complaint of buzzing and ringing in the ears or slight deafness after the labor. We tried 30 cases, omitting the quinin entirely, and found the omission of the quinin caused definite second stage and perineal delay. Dr. Losee, of the hospital laboratory, has now definitely proved the rectal absorption of quinin by its qualitative recovery from the urine in 45 out of 50 parturients.

A minimum of inhalation ether is needed for the delivery, and the anesthetist must be cautioned about this. Frequently no additional anesthesia is needed even for a perineorrhaphy. Chloroform should never be used with the ether rectal instillation. Gas, if

desired, is safe and very satisfactory as an adjuvant anesthetic for the delivery.

Relief of pain in labor is always open to two serious objections: the prolonging of the labor and the endangering of the safety of the mother or her baby. We believe this method, of all procedures we have so far studied, to be the least likely to prolong the labor if not used too early, and in over 2000 trials in the past two years to have been without danger to either mother or child. It can be used both in normal labors and in cases of dystocia, in labors induced with bags, in toxemias, in cardiacs and in women in labor with acute pulmonary conditions to whom inhalation anesthesia might be disastrous.

We find that it is applicable in hospital practice in 70 per cent of all labors. This is twice the applicability of scopolamin amnesia in our hospital experience ten years ago. Those not getting the rectal analgesia are largely on account of inexpedience, such as brief labors, admission with the head on the perineum or on account of some administrative interruption in the service. In other words, there is no obstetrical contraindication to the treatment after active labor is initiated. It can be used in the home with equal facility and with equally good results, and does not require the services of a trained anesthetist, especially taking the place of gas anesthesia in the last three hours of labor. The out-patient staff at the hospital are using it with good effect in the tenement confinements. It perhaps does not carry the patient along as thoroughly or as continuously as morphin-scopolamin amnesia, but it gives more relief than any form of inhalation analgesia with which I have had experience. It is not dangerous to the baby, though if pushed to the degree of complete anesthesia, which is not the desired object of the treatment, the baby may be born rather deeply anesthetized. We find no increase in operative deliveries; in fact in some comparative series it seemed proved that the use of forceps was decreased. There has been no increase of postpartum hemorrhage and no increase in the stillbirth rate.

There are certain occasional annoyances—I cannot call them disadvantages—of the method to which I must refer. Most of them are due to faulty technic. The most evident of these is occasional expulsion of the rectal instillation. Close attention to all the details of giving the retention enema will obviate its loss in bulk. The frequent extrusion of small quantities of light-yellow, sour-smelling liquid fecal matter, making it more difficult to keep the field clean in the perineal stage will not occur if the cleansing soapsuds enema is completely expelled before giving the rectal instillation. In some cases nausea is present, but not as commonly as after inhalation etherization. Patients at times will complain of a slight burning sensation in the anal region immediately after the rectal instillation. The liberal use of vaseline will prevent this,

though it sometimes may be due to an unrecognized fissure. Now and then there is some distention of the colon with gas but not to any serious degree. Rarely the patient has a diarrhea during the first twenty-four hours postpartum. I have already alluded to the occasional first stage of ether excitement but I have never seen it to the extent of requiring restraint.

There is never any tender induration after the magnesium sulphate injections such as we see after mercurial injections. To date there have been 5 abscesses. Two of them occurred when we were using 6 cc in bulk of the magnesium sulphate solution at one time, and 2 occurred after giving the injection in the thigh over the fascia lata, a location especially susceptible to abscess after any hypodermic. Considering the thousands of injections we have given, we are satisfied that, given intramuscularly with aseptic technic, the magnesium sulphate solution will rarely cause any abscess or necrosis *per se*.

If the primary injection of the morphin and magnesium sulphate is given too early it may temporarily stop the labor, but we have all seen morphin alone do the same thing when we have given it to ease the parturient's suffering while the cervix dilated. If this does occur, when the labor starts again the whole cycle of analgesia is started again, waiting until the pains recur at at least five-minute intervals and lasting over forty seconds, and the cervix is at least two finger tips' dilated before beginning again with the morphin and magnesium sulphate injection. Remember also to be very light with the inhalation ether at the perineal stage, as the patient goes under readily with a minimum amount and the baby may be born deeply anesthetized if much inhalation ether is given the analgesized mother.

Variations in the scheme will occur to men who use the rectal analgesia as their experience with it widens. With very large women, or when the ether instillations has no effect or even excites the patient and the birth is anticipated within two hours, a second instillation of one-half the original amount may be given at once. At times in nervous primiparæ, or where for some reason we would like to start the analgesia before the pains and the cervical dilatation had attained the desired stage, $\frac{1}{8}$ gr. of morphin can be given with the first 2 cc of magnesium sulphate solution, and in one-half hour a second $\frac{1}{8}$ gr. of morphin with the second 2 cc of magnesium sulphate, then waiting for the strong pains and three finger tips' dilatation of the cervix before giving the ether instillation by rectum.

Summary. We are convinced that this is the safest and most effective method for the relief of the pains of childbirth over a period of hours that has so far been devised. Its applicability is much greater than that of scopolamin amnesia. It can be used safely and effectively by the physician in home confinements, and does not require the services of a trained anesthetist. The drugs

required, morphin, magnesium sulphate, ether and quinin, are easily obtained and well known in their action. The quinin is found to be an essential ingredient in the rectal instillation formula. The only contraindication to the procedure is uterine inertia, and the only restriction is not to start too soon. The woman must be in active labor, that is, pains every five minutes, lasting forty seconds by the watch, and in a primipara preferably the cervix should have attained a dilatation of two or more finger tips. The mechanism of labor must be as closely followed by the obstetrician as if no analgesia were being employed.

This method of analgesia and amnesia does not carry the parturient woman entirely over the valley of her suffering on any soft couch of unconsciousness, and it would be a great mistake to believe it did or to promise her that it would. But we do feel assured that we have here a method of real value that will abolish the most dreadful part of the ordeal of labor in almost all cases, that it is without danger to either the mother or her baby, and that in painstaking hands by strictly adhering to the described technic, even its occasional annoyances may be avoided.

REPORT OF AN INTERESTING TYPE OF DIAPHRAGMATIC HERNIA OF THE CARDIA OF THE STOMACH THROUGH THE ESOPHAGEAL ORIFICE.*

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HERNIA through the diaphragm is a deformity which has always attracted much interest. Ambroise Paré¹ was the first, in 1610, to describe 2 cases due to trauma; following this publication Fabricus Hildamus² reported another instance in 1646. The first congenital case noted in literature was observed by Riverius,³ in 1698, and Kirschbaum⁴ described this condition exhaustively in 1755, reporting 17 cases. Later (1769) Morgagni⁵ published a monograph on diaphragmatic hernia and Sir Astley Cooper⁶ presented an interesting account of this affection in 1824. More recently Bowditch⁷ (1853) contributed a valuable monograph on this subject, collecting 88 cases from the literature.

* Read by title at the Meeting of the Association of American Physicians held in Washington, May 7, 1925.

The most satisfactory classification of diaphragmatic hernia, as described by Richards,⁸ is as follows:

I. True hernias (those with hernial sac).

1. Congenital.

2. Acquired.

(a) Through the natural openings (esophageal).

(b) Elsewhere (traumatic or nontraumatic).

II. False hernias (those without hernial sac).

1. Congenital.

2. Acquired (all traumatic).

III. Eventration of diaphragm.

The various locations for diaphragmatic hernia may be divided, according to Richards, into anterior, central, posterior, esophageal and others.

1. ANTERIOR. These forms of hernia, also known as parasternal hernias, are located on either side of the attachments of the diaphragm to the sternum and are produced through Larry's space, or the foramen of Morgagni.

2. COSTAL. This form of hernia may or may not present a sac and appears at areas not related to the fusion lines of those parts combining to form the diaphragm.

3. POSTERIOR. These are largely due to an absence in the closing of the pleuroperitoneal canals, and originate in the lumbar region at or near the foramen of Bochdalecki.

4. ESOPHAGEAL. This is a very frequent site for diaphragmatic hernia. It is due to the failure of the muscle surrounding the diaphragm to closely encircle the esophagus. These hernias are frequently the true forms, the sac being formed of part of the diaphragm attached to the esophagus.

5. OTHER SITUATIONS. Of less frequent occurrence are those forms that have their exit by way of entrance of the sympathetic nerves in the crura of the diaphragm.

It is neither our object in this communication to discuss the various forms of diaphragmatic hernias, nor indeed those occurring through the esophageal hiatus in which a large part or the whole of the stomach is found in the thoracic cavity, but to limit our attention to that type in which the cardia of the stomach in part or in whole has herniated through the esophageal opening. Hernia through the esophageal hiatus is not uncommon, and occurs more frequently than any other form. In most instances the stomach enters the left chest or posterior mediastinum covered by a hernial sac. In the vast majority of cases reported the whole or a large part of the stomach, and even the other abdominal viscera may be included. Abbott⁹ has recently called attention to the true but small hernias of the diaphragm, especially of the periesophageal type, which may be detected in the early stages, and in which the cardia is alone involved, and Morrison¹⁰ has pointed out the method

of diagnosis by means of roentgenology. Many of these hernias are acquired and are produced by unusual strain or coughing. They are frequently only detected by means of fluoroscopy.

Of interest in regard to this special type of hernia is the following observation of Andrew¹¹ made in 1903 on a case discovered in the dissecting room of Aberdeen University, which represents the first case published of diaphragmatic hernia of the cardia, through the esophageal opening.

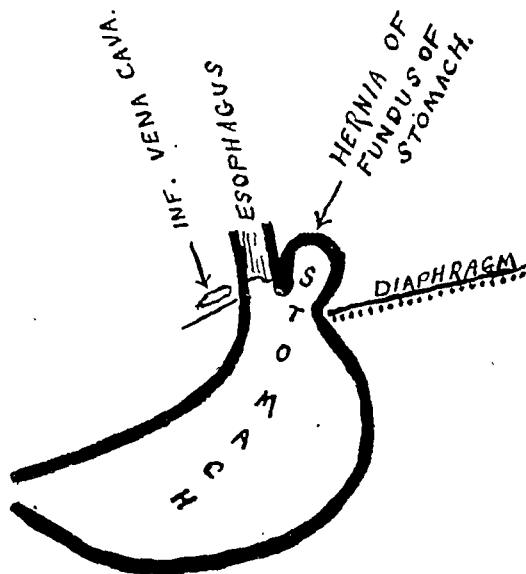


FIG. 1.—Diagrammatic drawing showing herniated fundus of stomach through the esophageal opening.

The patient was a female in whom the stomach presented a hernia at the cardiac orifice. Immediately to the left of the esophageal opening there was a dome-shaped pouch of the diaphragm into which a finger could easily be passed, and drawn up into this was part of the cardiac end of the stomach measuring vertically about an inch. The herniated cardia could easily be pulled down from this pocket, when it was noticed that the part of the stomach wall which lay against the neck of the pouch was thickened. The peritoneum was reflected from the diaphragm to the stomach at the top of the pouch.

There were 6 cases of diaphragmatic hernia of the cardia of the stomach through the esophageal orifice in our series. These were all observed in females, the ages ranging between forty-one and sixty-two years. The symptoms noted were quite similar to those which will be referred to later, and the diagnosis was definitely established by means of the roentgen-ray which revealed the typical picture of this anomaly.

The following notes briefly describe the salient features of our cases:

Case Reports. CASE I.—July 18, 1924: M. M., a female, aged sixty-two years, was referred to us by Dr. I. Pels. She was affected with an extensive lupus erythematosus for the past ten or eleven years. There was present, in addition, marked indigestion. Eight years ago the patient had been subjected to severe attacks of abdominal colic occurring in the upper right quadrant of the abdomen, for which hypodermatic injections of morphin became necessary for relief. She now complains of abdominal pain, noted especially in the left upper quadrant and in the epigastrium, loss of appetite, nausea, acidity, eructations, regurgitation of food, occasional vomiting and constipation. These symptoms are more prominent following full meals, and occur more frequently at night after the patient has retired.

On examination the chest organs were found normal. The abdomen was distended and the liver was somewhat enlarged and tender on pressure. The test meal presented a total acidity of 33; free hydrochloric acid, 22.

The roentgen-ray report is as follows: The heart and lungs are negative. The esophagus presents a slight retardation of the meal at the cardia. The stomach is in normal position, and held slightly to the right; peristalsis is normal. A shadow is noted at the cardia, extending into the chest, passing through the esophageal orifice, indicating the presence of a hernia; no filling defect is revealed. The pylorus and the duodenal cap are normal. The liver is slightly enlarged and the colon moderately prolapsed.

CASE II.—October 17, 1924: M. S., a female, aged fifty-three years, had been the subject of nervous and hysterical attacks for a long time. During the past year there has been marked indigestion in the form of pain in the epigastrium and immediately above the ensiform cartilage, with a burning sensation in the stomach occurring about an hour following meals. There were present acid eructations, loss of appetite, regurgitation of food and constipation. The symptoms were aggravated in the recumbent position, especially following large meals. Occasionally dysphagia was noted, and a sensation of a lump moving up and down during deglutition was experienced. This patient has lost 35 pounds in weight.

On examination the chest organs are found normal. The abdomen is relaxed and soft, and no masses or tender areas are noted. The gastric secretion presents a total acidity of 34; free hydrochloric acid, 20.

The roentgen-ray examination reveals the heart and lungs to be negative. The stomach is in normal position and peristalsis is normal; no filling defects are noted. In the recumbent position a small pouch of the cardia of the stomach is observed above the diaphragm, passing through the esophageal orifice. The lower end of the esophagus is observed behind and to the right of the herniated

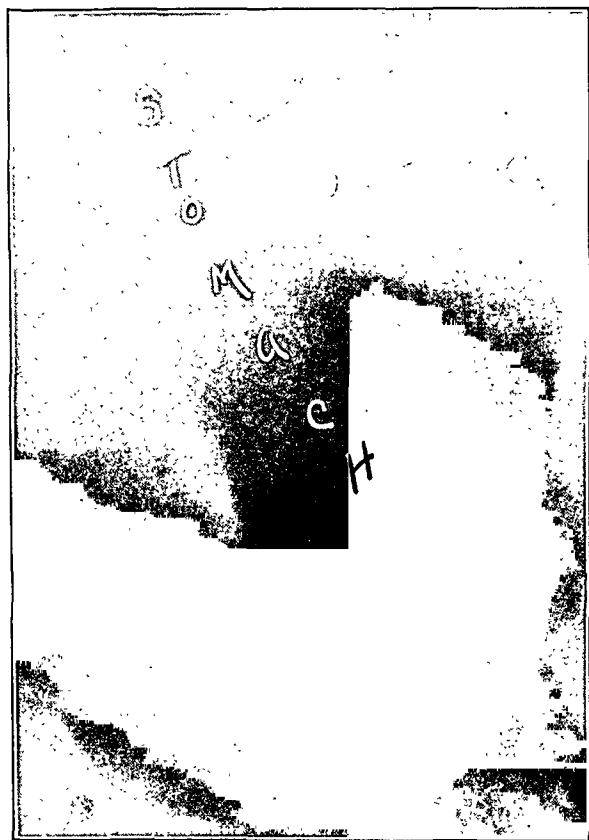


FIG. 2.—Case No. V. Showing hernia of the stomach, esophagus to right of stomach.



FIG. 3.—Case No. II. Hernia of the stomach, esophagus to right of hernia.



FIG. 4.—Case No. IV. Showing herniated stomach above diaphragm, esophagus behind hernia.

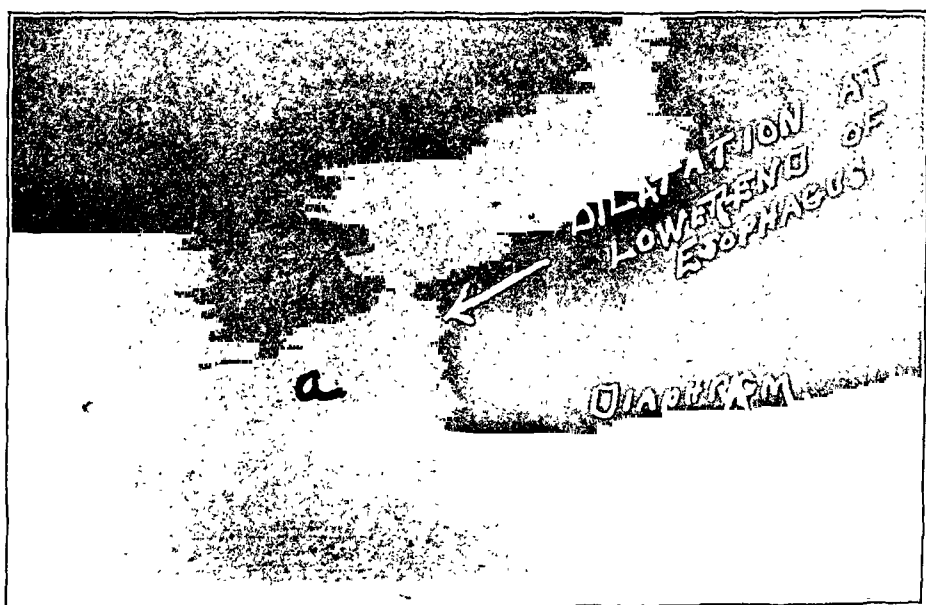


FIG. 5.—Showing a small circumscribed dilatation (a) at lower end of esophagus, due to a stricture and ulceration, simulating hernia of the stomach through the esophageal opening.

cardia. The pylorus and duodenal cap are normal. The liver extends to the costal margin. The colon is moderately prolapsed.

CASE III.—November 5, 1924: N. C., a female, aged forty-two years, had been affected for a number of months with discomfort in the epigastrium just below and above the ensiform cartilage. At times actual pain is experienced, especially following a heavy meal; and during the night the discomfort is often sufficiently severe to awaken the patient. She is also affected with acidity of the stomach; regurgitation of food and occasionally vomiting, dizziness and constipation. Dysphagia has frequently occurred, especially in the early morning and following food.

On examination the thoracic organs are found to be normal. The abdomen is relaxed, the edge of the liver being just palpable; no tenderness is noted anywhere except slightly in the upper left quadrant. The gastric secretion presented an achylia; total acidity, 33; free hydrochloric acid, 0.

The roentgen-ray examination is as follows: The esophagus presents a slight retardation of the barium meal at the cardiac orifice. The stomach is in normal position; the pylorus and duodenum are normal. In the recumbent posture the cardia of the stomach is observed to pass up through the esophageal orifice on deep inspiration, which disappears when the patient is in the upright position.

CASE IV.—December 12, 1924: C. S., a female, aged fifty-six years, has complained for the past year of pain in the epigastrium and of indigestion occurring about an hour following meals. There is marked acidity and regurgitation, and the symptoms frequently become aggravated at night during the sleeping hours. Difficulty and pain in deglutition are occasionally noted. On account of these symptoms, together with a painful epigastric area, a diagnosis of ulcer was made; however, no improvement followed the institution of an ulcer treatment.

On examination the chest organs are found to be normal. The abdomen is soft; the edge of the liver is palpable, and there is an exquisitely tender area in the epigastrium just below the ensiform cartilage and a slight tenderness is also noted under the right costal arch. The gastric secretion shows a total acidity of 55; free hydrochloric acid, 36.

The roentgen-ray examination reveals a slight retardation of the barium meal at the cardia; no irregularity of the lumen of the esophagus is noted. In the recumbent position the cardia of the stomach is observed passing up through the esophageal opening only, however, in deep inspiration, or on straining, the meal passing behind the shadow. The hernia is absent in the upright posture.

CASE V.—January 5, 1925: J. I. G., a female, aged forty-one years, for some months following an indiscretion in diet, has complained of discomfort in the lower left chest and epigastrium, occurring especially one-half to one hour following meals. In addition, dysphagia, nausea, acid eructations, flatulency and constipation have occurred at times.

On physical examination the thoracic organs are found to be normal. The abdomen is distended; there are no enlargements. There is a slight tenderness noted on pressure above the ensiform cartilage, extending into the epigastrium.

The gastric secretion reveals a total acidity of 40; free hydrochloric acid, 25.

The roentgen-ray presents a slight retardation of the barium meal at the cardia. The stomach shows normal peristalsis, and the pylorus and duodenal cap are normal. In the recumbent posture the cardia of the stomach is observed as a hernia through the esophageal hiatus about the size of a silver dollar. It becomes more marked on deep inspiration and disappears in the upright position. The meal can be detected passing around the herniated shadow.

CASE VI.—April 2, 1925: N. C., a female, aged fifty-three years, had a cholecystostomy performed six years ago, and a cholecystectomy four years. She has since been affected with eructations of gas, pyrosis, distention in the upper abdomen appearing especially about two hours following meals. Attacks of pain occur most severely at 11 P.M. and 2 A.M. The symptoms become markedly aggravated by a heavy diet, especially when the latter consists of meat. The patient is extremely neurotic.

On physical examination the thoracic organs are found negative. The abdomen is markedly distended and very pendulous. There is a slight epigastric pulsation, with tenderness over the entire abdomen, but especially noted in the left upper quadrant.

The roentgen-ray report is as follows: The heart and lungs are negative; the esophagus is normal, with the exception of the presence of a patent cardioesophageal opening. In the recumbent posture the opaque meal passes quickly down through the esophagus. On deep inspiration, a small knuckle of the cardia is also noted passing through the esophageal hiatus under similar conditions. The hernia disappears in the erect posture.

These small hernias give rise to a train of symptoms suggesting this anomaly with signs somewhat pointing to gastric ulcer or cholelithiasis. These consist of epigastric pain or pain immediately above the ensiform cartilage associated with acid eructations, regurgitation and vomiting. The symptoms are more frequent following the ingestion of large meals and occur more often when the patient assumes the recumbent posture after eating. The discom-

fort may be especially severe at night, causing the patient to be suddenly awakened from sound sleep. Dysphagia is not infrequent, especially early in the morning, and there is often a sensation as if food were passing part way up the esophagus and then to return again. The pain appears usually an hour or two following meals, especially on reclining, and is relieved temporarily by means of alkalies. It often radiates to the back between the shoulder blades. The disappearance of symptoms for variable periods may erroneously point to ulcer, while the acute pain radiating to the back may suggest cholelithiasis.

The diagnosis may be definitely established by means of the roentgen-ray examination which presents a very characteristic picture. However, in the routine examination of the gastrointestinal tract this type of hernia may be entirely overlooked unless a special technic be instituted. The patient is at first fluoroscoped in the upright posture. The opaque meal is carefully observed as it descends through the esophagus. A slight retardation of the meal may be noted at the cardia in some instances. The lumen of the esophagus, however, appears quite normal. In this condition the stomach is situated largely to the left and usually high under the left side of the diaphragm, and is of the cow-horn or modified cow-horn type. In the upright position no abnormality is noted, and no clue as to the actual condition is obtained. In the examination the patient is placed in the recumbent posture in various positions in order to obtain the clearest view of the cardio-esophageal opening. Even under those conditions, however, the hernia through the esophageal opening may not become visualized until rapid and deep breathing has been practised. Under certain conditions it may also be advisable to have the patient strain. By means of this method, due to the more constant filling of the fundus the herniated area becomes more easily visualized.

On expiration the opaque meal may be noted passing back into the stomach below the diaphragm. In our cases a portion of the fundus of the stomach was observed passing up through the esophageal opening through the diaphragm on deep inspiration, and then only when the patient maintained the recumbent posture. The size of the hernia varied in our cases from that of a chestnut to a small orange. A fluid level or a bubble was frequently present, but was ordinarily noted in most instances after the diagnosis of hernia had been established. The contour of the herniated fundus is usually smooth and regular in appearance. This form of hernia occurs to the left of the esophagus and may not be visualized in every examination. The constancy depends largely upon several factors; (1) Upon the size of the esophageal orifice; (2) upon the muscular contraction around the esophageal opening; (3) upon the position of the patient; (4) upon deep inspiratory movements; (5) upon the special roentgen-ray technic described above. According

to Morrison,¹⁰ the cardioesophageal opening is usually patent in this condition, though this only occurred but once in our series. Neither stasis in nor strangulation of the herniated sac was noted in any of our cases.

In the diagnosis of diaphragmatic hernia of this type other affections simulating this condition must be ruled out. On this account the patient is given another opaque meal through a straw while in the recumbent posture, and the esophagus is examined under the fluoroscope while swallowing the barium mixture. By means of this method it is a simple matter to ascertain the relation of the herniated fundus to the esophagus. The esophagus is observed on either side or posterior to the hernia. In establishing the diagnosis this procedure is of great importance.

At times a small circumscribed dilatation at the cardiac orifice of the esophagus will simulate this condition. However, under the fluoroscope the dilatation is observed within the esophagus and above the diaphragm while the patient remains in the recumbent posture. Obstruction may be present, though this condition was not observed in a case presenting a small dilatation in our clinic in which the shadow was situated directly above the diaphragm, resembling a hernia in many respects.

Again, when patency of the cardioesophageal opening occurs, which is also best noted in the recumbent posture, the opaque meal will be observed passing up the esophagus on deep inspiration, the stomach appearing below the diaphragm.

A diverticulum at the lower end of the esophagus also may be confused with this form of hernia. The pouch may be observed budding off from the esophageal wall and the filling takes place directly from the esophagus. A gastric diverticulum as a pouch protruding from the wall of the stomach when occurring directly below the diaphragm also may resemble this condition.

The form of thoracic stomach as described by LeWald¹² must not be confused with diaphragmatic hernia of this type. In this condition the esophagus is shortened and never passes through the esophageal opening while the stomach remains constantly in the thoracic cavity.

Conclusions. 1. There exists a form of hernia of the cardia of the stomach, through the esophageal opening, in which this area is alone involved, producing a rather characteristic picture which may even be demonstrated in its early stages.

2. These hernias often give rise to a train of symptoms suggesting atypical forms of ulcer or cholelithiasis.

3. The diagnosis may be definitely established by means of the roentgen-ray, which presents characteristic signs only; however, when the patient is examined in the recumbent posture in deep inspiration or on straining.

4. In all cases presenting atypical signs of ulcer or cholelithiasis a thorough investigation should be instituted in order to determine the possibility of the presence of this condition.

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IODIN HYPERTHYROIDISM.

CONCLUSIONS BASED ON A STUDY OF 38 CASES.

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THE popular enthusiasm which has supported the prophylactic treatment of simple colloid goiter, together with the discovery of the efficacy of iodine in the treatment of exophthalmic goiter, has greatly increased the number of cases of iodine hyperthyroidism in this country within the past two years. Between January, 1923, and January, 1925, 38 cases of iodine hyperthyroidism have been observed in our Clinic. Of this number 20 have been observed during the last six months. In view of the apparently rapidly increasing number of patients observed with this condition, attention should be directed to the danger in the use of iodine, as well as to its beneficial effects in the treatment of goiter. I have felt this more keenly than ever since my recent observation of 2 patients, whose death was directly due to the ingestion of iodine. Moreover, many of these patients have been brought through their serious conditions with the greatest difficulty.

Etiology of Iodine Hyperthyroidism. Although the beneficial effects of iodine in the treatment of goiter have long been realized, it remained for Kocher to call attention to the possible dangers in this form of therapy. Röser, Prévost, Lebert and others believed

that hyperthyroidism was caused by the softening of the goiterous tissue and not by iodine intoxication; but this view was not accepted at once. Rilliet described a syndrome which he termed *constitutional iodism* and considered due to certain goiterous subjects receiving iodine. Because in many ways this condition resembles exophthalmic goiter, or Basedow's disease, Breuer called it "iodine-Basedow," and it has since generally been termed by that name. From time to time mention has been made in the literature of the danger of using iodine promiscuously in the treatment of goiter, and occasional reports of isolated cases appeared. Recently I made a preliminary report of 18 such cases studied over a brief period of time.⁴ The rapidly increasing number of these patients at present justifies a more careful study and a detailed report.

In considering the question of etiology, it has been noted that many kinds and preparations of iodine have been responsible for the development of iodine hyperthyroidism. The various liquid forms of the syrup or tincture, preparations containing ferrous iodide, or the tablet form have all been used. There have been interesting observations regarding the dosage. Apparently some persons have a relative immunity to iodine hyperthyroidism, since iodine administered in moderate or even large doses for weeks or months causes no toxic symptoms. Others develop toxic symptoms very rapidly after the ingestion of small doses or after only a few weeks' administration. I have been surprised in many of my cases at the small amount of iodine necessary to initiate toxic symptoms.

The Pro and Con of General Distribution of Iodine. The variable quantity of iodine necessary to produce toxic symptoms in persons with adenomatous goiters brings up the question of the advisability of the wholesale distribution of iodine by way of drinking water or table salt. The Michigan State Board of Health, after a very careful analysis of the problem has given every school child this year iodized salt.

Certain cities, for example, Rochester, New York, Minneapolis and Chicago, have considered putting iodine in the city drinking water. As a means of preventing the further development of goiter, and as a method of combating the colloid goiter now in existence, these methods are certainly a step in the right direction. One question, however, naturally arises: What effect will this wholesale use of iodine have on the hundreds of thousands of persons with adenomatous goiter now living in the goiter areas. It is contended by some that the amount of iodine these persons would receive would be too infinitesimal to produce any harmful effect. Others go so far as to say that the great good that would result would outweigh any harm that might be done. It is also contended that since goiter does not occur in the south where iodine is prevalent in the water, an effort should be made to rectify the conditions in the goiter areas and change the iodine content of the water at once.

The objection to the distribution of iodine in the form of salt is that the dosage is very inaccurate. Some children use a great amount of this commodity, while others use but little. A child may take a great deal of salt one day and then go several days without any. If salt is employed in the cooking, as is advocated by some, any or all members of the family will receive iodine in various amounts.

De Quervain believes that the general prophylaxis by means of cooking salt, so as not to be harmful to adults with goiter, should be restricted to a minimum dose, even though it be insufficient for an infant already affected. He is opposed to the free distribution of iodine, as there is great risk of "Graves' disease."

With regard to supplying iodine through the drinking water, O. P. Kimball writes: "Following the publication by McClendon last spring of his findings regarding the deficiency of iodine in the water, the Department of Health of Rochester, N. Y., attempted to iodize the city water supply by the addition of such an amount of sodium iodide as would make each 5 gallons of water contain 1 mg. of sodium iodide. This method had often been discussed, but it had never been considered practicable because of the great waste. For instance, only approximately one-fourth of 1 per cent of the city's water supply, not more than 4 ounces, is actually imbibed, and not more than 15 per cent of this 4 ounces is really needed. That means that the city is paying \$450.00 for a needed 5 gm. of sodium iodide."

Whether or not such small doses of iodine are sufficient to initiate symptoms of hyperthyroidism in cases of nontoxic adenoma is a debatable problem. Careful study and detailed reports on all such cases as may be observed will solve this question.

Effect of Iodine in Various Types of Goiter. We know from the experience of Marine and Kimball, as well as that of others, that iodine administered to children under twenty years of age for the prevention or treatment of colloid goiter is practically harmless when given in small doses. During the past three years I have had over 300 cases of colloid goiter in children under observation, and there has been no instance of the development of toxic symptoms.⁵ When iodine is administered in the presence of an adenoma in children I believe great care must be exercised. I frequently give iodine in such cases with no hope of eradicating the adenoma but merely with the idea of retarding its growth by putting the gland at rest until the patient has reached the age of twenty-one years. Although I never give these patients more than 10 mg. of iodine a week, I have had 2 cases of beginning hyperthyroidism which were aborted by discontinuing the iodine at once and placing the patient at rest. I have observed several other patients treated elsewhere with much larger doses of iodine. One of these was a girl, aged fifteen years, who lost 30 pounds in two months and had a metabolic

rate of +45 per cent. I performed a thyroidectomy after medical measures had failed, and she made an excellent recovery.

On the whole, iodine hyperthyroidism is rarely observed in persons under thirty years of age. I believe that iodine is of no avail in treating goiter, except the exophthalmic type, after the age of twenty-one years, and that with increasing age it is employed with added risk.

Iodine is certainly very definitely contraindicated after the age of twenty-one years, in the presence of an adenomatous goiter. Yet, there are now thousands of persons with this form of goiter who are taking iodine either by means of some patent medicine, or, alas, under a physician's directions. The newspapers and magazines are so full of articles on iodine and goiter that the laity has come to consider one a cure for the other. Every patient who has a goiter comes to the physician with hopes of a cure by iodine. In many cases the physician fails to distinguish between a colloid and an adenomatous goiter, or even between an adenomatous and an exophthalmic goiter. If a slight reduction in the size of the neck through the effect of iodine on the colloid occurs, there is such gratification that the symptoms of developing hyperthyroidism are overlooked.

Differential Diagnosis of Adenomatous and Exophthalmic Goiter. The term iodine-Basedow, as applied to the peculiar syndrome developing from the injudicious use of iodine in the treatment of goiter, is not a correct one in the light of our present knowledge of the subject. At the time when Breuer described this condition, no attempt had been made to distinguish between the form of hyperthyroidism occurring in exophthalmic goiter, or Basedow's disease, and the hyperthyroidism of toxic adenoma. It was not until 1913 that Plummer pointed out the chief differences between the two conditions.

Whereas, exophthalmic goiter is a disease of rapid onset, averaging nine months' duration and occurring most frequently in young persons, toxic adenoma is a chronic condition averaging four years in onset and occurring as a rule in persons more than forty years of age. In exophthalmic goiter the symptoms of hyperthyroidism progress by series of waves at the crests of which all the symptoms are exaggerated and a crisis occurs. In toxic adenoma the hyperthyroidism progresses insidiously and slowly, causing a permanent damage to the heart, kidneys and other organs. There is a rapid loss of weight and strength, accompanied by a variable appetite which, in exophthalmic goiter, at times is ravenous. Likewise, examination reveals exophthalmos in fully 50 per cent of the cases within three months of onset. The gland is symmetrically enlarged and thrills and bruits may be detected in 80 per cent of cases. Exophthalmos does not occur in adenomatous goiters; the gland is asymmetrically enlarged; thrills and bruits are seldom noted.

Hypertension occurs in this type of goiter with a proportionately high diastolic pressure, in contrast to a slightly elevated systolic and a low diastolic pressure in exophthalmic goiter. In adenomatous goiter, not only is there slow development of the toxic symptoms, but there is usually a history of goiter of sixteen years' duration or more. The metabolic rate is considerably lower, seldom rising above + 60 per cent, while in exophthalmic goiter we not infrequently see rates above + 100 per cent.

Syndrome of Iodin Hyperthyroidism. The syndrome of iodine hyperthyroidism is not typical of either adenomatous or exophthalmic goiter, and yet presents many symptoms common to both. It may develop in children as young as ten years or in elderly persons who have adenomatous goiter. It is uncommon before the age of thirty years, the average age of the patients in this series being thirty-five years. The same tremor, loss of weight and strength, tachycardia, restlessness and insomnia occur, as in the two types just described. The onset of symptoms and the loss of weight are more rapid and severe than in toxic adenoma, and thus iodine hyperthyroidism rather closely resembles exophthalmic goiter. The peculiar type of nervousness, at times approaching delirium, is also like that of exophthalmic goiter. The average duration of symptoms in this series was about three months.

Two patients in this series lost more than 50 pounds in two months. The ravenous appetite characteristic of exophthalmic goiter does not occur. Tachycardia is severe and persistent, and there is little or no response to digitalis. Apparently the iodine exerts a toxic, antagonistic effect on the myocardium that renders it immune to the action of this drug. The pulse often rises above 150 after thyroidectomy and is the source of much concern. Thrills, bruits and exophthalmos do not occur in these cases. The pulse pressure is elevated, but the blood-pressure findings closely resemble those in toxic adenoma. The same is true of the basal metabolic rate, the average in this group being + 31 per cent as compared with + 29 per cent in a group of cases of toxic adenoma and + 54 per cent in a series of cases of exophthalmic goiter.

Treatment of Iodin Hyperthyroidism. If iodine hyperthyroidism is diagnosed early in its course, it is possible to abort the toxic symptoms. Three of the patients here reported were cured by medical measures, while the rest were relieved only by thyroidectomy. If the symptoms are not becoming progressively worse every effort should be made to improve the patient's condition first by medical means.

Operation in cases of iodine hyperthyroidism is frequently performed with considerable risk. One patient (No. 42044) was delirious for a week following operation. Another (No. 42282) gave a history of having been given iodine for four months by a physician. During the two months preceding and following child-

birth she lost 55 pounds. She was admitted in a state of delirium, running a temperature of 102°C . and a pulse rate of 140. After two



FIG. 1.—Case No. 42044. Gross specimen, showing areas of colloid with multiple degenerating adenomas of the thyroid. The absence of the typical, beefy appearance of a hyperplastic gland is evident.

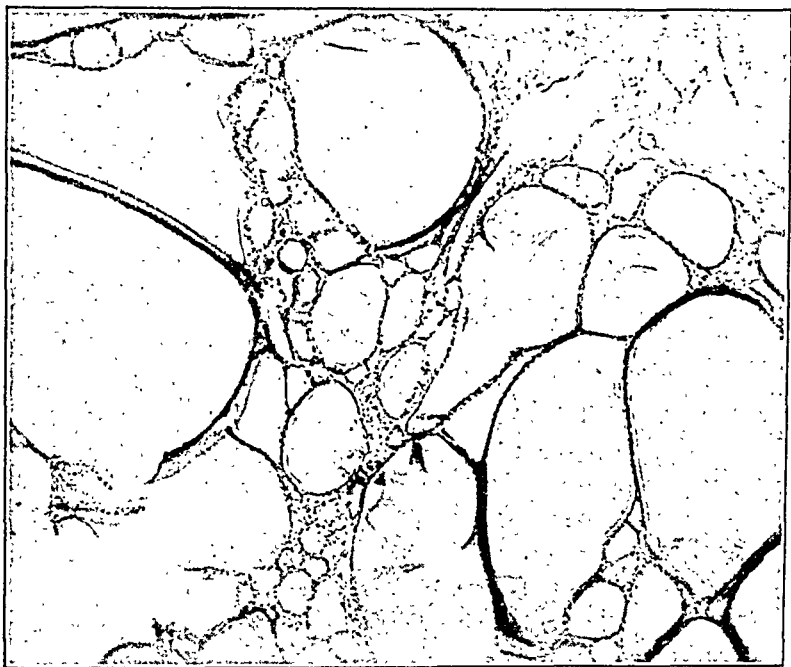


FIG. 2.—Case No. 42282. Large areas of colloid in an adenomatous thyroid. The apparently benign appearance is in no way indicative of the severe clinical picture of hyperthyroidism induced by iodine with fatal termination.

weeks' treatment there was marked improvement, only to be followed by a more critical course. Thyroidectomy was attempted as a last resort, but a fatal termination followed three days later,

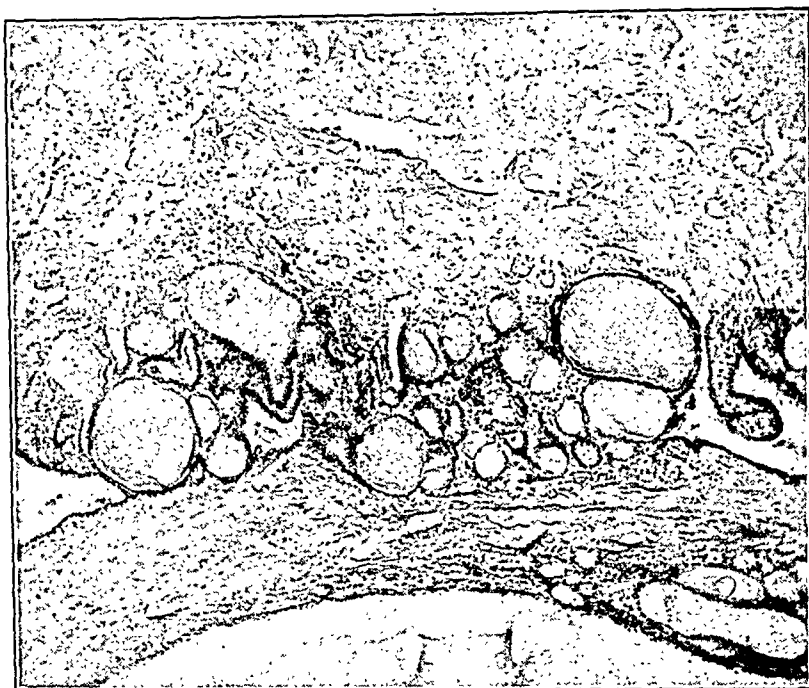


FIG. 3.—Case No. 42282. Degenerating, fibrous, hyalin adenoma with areas of colloid. The clinical picture was one of extreme hyperthyroidism, with delirium, marked tachycardia and emaciation accompanied by gastrointestinal crises. The basal metabolic rate of + 54 did not indicate the severity of the disease.

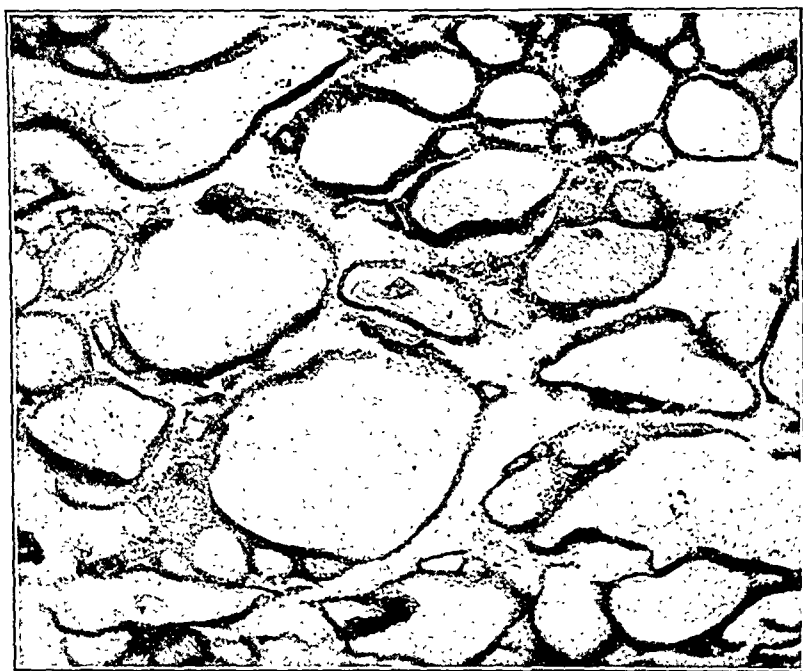


FIG. 4.—Case No. 30262. Apparently large areas of colloid in an adenomatous goiter. Close inspection reveals a small amount of hypertrophy, but the typical columnar cells of exophthalmic goiter are absent. The clinical findings in this patient were somewhat suggestive of the latter condition, but the history of the ingestion of iodine under a druggist's prescription for several months confirmed the diagnosis of iodine hyperthyroidism.

This patient remained in delirium; the pulse continued irregular and never fell below 150.

A careful pathological study as usual in these cases failed to reveal any of the typical findings of exophthalmic goiter. There were no areas of hyperplasia and only the typical appearance of an adenomatous goiter with areas of colloid was observed.

The prognosis in iodine hyperthyroidism following thyroidectomy is excellent in the early cases, inasmuch as little permanent damage has been done to the heart and other vital organs.

Typical Case of Iodine Hyperthyroidism. CASE 42044.—A man, aged sixty-four years, came to our clinic complaining of stomach trouble. The symptoms were of three months' duration, and dated from an accident in which he had been run over by a side delivery rake and painfully bruised. Since then he had had frequent spells of vomiting during or immediately after eating. Sweet foods had caused the most trouble. The vomiting had been increasing in severity and frequency. No hematemesis or melena had been noted and he had had no pain. He had lost between 40 and 50 pounds in two months, and had become too weak to walk. Increasing nervousness had been noticed, with palpitation of the heart, especially on lying down. After some hesitation the patient admitted having taken ten bottles of Allen's Goiter Cure during the past three months.* The patient had noticed a goiter for three years and sought to cure it by this method.

Physical examination revealed an emaciated elderly man whose restless, nervous, uncoöperative manner at once suggested the picture of hyperthyroidism, but was characteristic neither of that of toxic adenoma nor of exophthalmic goiter. (There is something about the lack of mental coördination and nervous instability in these cases verging on or into actual delirium, together with a sort of apathy that causes the patient to moan repeatedly and lose all mental control that serves to distinguish them from the nervous disturbances occurring in the other types of hyperthyroidism.) A rather large, multiple adenomatous goiter was visible. Edema of the legs was evident. Exophthalmos was not noted. The skin was warm and moist, and there was a coarse tremor of the fingers.

Examination of the thyroid revealed no thrills or bruits and resulted in the diagnosis of a multiple adenomatous goiter with a substernal projection on the right side. The heart was enlarged 2, on a scale of 1, 2, 3, 4. There was a hemic murmur at the apex and evidence of myocarditis and decompensation. The pulse was 130, and there was a marked arrhythmia, as frequently noted in these cases. The liver border was slightly enlarged; there were a

* The writer sent a bottle of this remedy to the Propaganda Department of the American Medical Association in 1923. Investigation in the Association's chemical laboratory revealed that the nostrum consists essentially of ferrous iodid and hydriodic acid in syrup.

few moist rales at both bases of the lungs posteriorly; the abdomen was negative on palpation. With the exception of infected teeth, the physical examination was otherwise negative. The blood pressure was 160 systolic and 66 diastolic; a high pulse pressure with the systolic normal and the diastolic decreased.

A tentative diagnosis was made of iodine hyperthyroidism in an adenomatous goiter.

Roentgen-ray examination of the stomach was negative. The urine was normal, save for hyaline casts, 1. Examination of the blood was negative. The basal metabolic rate was + 67.

In the hospital proctoclysis was employed and subcutaneous injections of saline were administered in an effort to dilute the toxins and to combat the dehydration. Digitalis was prescribed. Although it has been repeatedly noted that digitalis has little effect on the pulse rate, it may strengthen the cardiac muscle. Luminal and chloral were used to combat the nervousness. Little or no improvement was noticed at the end of ten days, except that the vomiting was controlled; there was no dehydration; the mental attitude was better. Nothing was to be gained by delaying operation further.

Thyroidectomy was performed under the usual morphine-scopolamine-novocaine method of anesthesia. The patient, however, was not as quiet and cooperative as patients with other types of hyperthyroidism. As usual, following operation in these cases the pulse became extremely rapid, remaining as high or higher than 150 for four days. Arrhythmia persisted for two weeks. For a week the patient was delirious much of the time. The temperature, however, differed from that customarily observed in cases of post-operative hyperthyroidism in exophthalmic goiter, and did not rise above 102° C.

Two months later the patient had regained 20 pounds; his strength had returned; the pulse rate was 80; the nervousness had disappeared. Save for slight edema of the ankles, he was apparently well.

Pathology. Medical literature contains little that is enlightening concerning the pathology of the thyroid gland in cases of hyperthyroidism induced by iodine. Crotti makes the following statement with which I cannot agree. "We know that in iodine-Basedow the histological changes are the same, as the ones seen in any other form of toxic or bacterial thyroiditis. Hyperemia of the gland takes place; cellular hypertrophy and hyperplasia occur; the thick colloid, rich in iodine, undergoes liquefaction and is quickly absorbed and thrown into the circulation under the form of an iodized albuminoid substance, mostly thyroxine."

A careful pathological study of my cases failed to reveal the occurrence of cellular hypertrophy and hyperplasia. Instead of the colloid being absorbed, it is evident from the microphotographs,

as well as the gross specimens, that unusually large areas of colloid are present in the thyroid. The typical multiple adenomatous goiter was found, with degenerating and degenerated cystic, fibrous, hyalin and calcareous adenomas. In three of the sections minute areas of hyperplasia containing cells of the columnar type, such as may be seen in cases of toxic adenoma of the thyroid, were present.

MEDICAL AND SURGICAL RESULTS IN TREATMENT OF IODIN
HYPERTHYROIDISM.

Case No.	Sex.	Age.	Iodin, months.	Prescribed by.	Basal metabolic rate.	Loss in weight in pounds.	Treatment.	Basal metabolic rate on discharge.	Gain in weight.
32444	F.	65	3	Fam. phys.	+29	10	Thyroidectomy	+5	40
32860	F.	28	5	Fam. phys.	+17	12	Thyroidectomy	+1	24
31732	F.	30	2	Fam. phys.	+20	25	Thyroidectomy	+4	8
29894	F.	36	3	Fam. phys.	+44	29	Thyroidectomy	+10	25
30160	F.	34	2	Fam. phys.	+13	16	Thyroidectomy	+4	28
33276	F.	27	3	Surgeon	+22	15	Medical	+4	5
33663	F.	53	2	Fam. phys.	+29	30	Thyroidectomy	+0	50
33275	F.	23	2	Internist	+16	8	Thyroidectomy	+4	14
34808	F.	35	2½	Quack remedy	+31	13	Thyroidectomy	+8	22
29598	F.	50	3½	Specialist	+46	15	Thyroidectomy	+4	18
34592	F.	32	4	Quack remedy	+24	10	Medical	+8	12
35087	F.	40	3	Fam. phys.	+18	30	Thyroidectomy	+4	16
35365	F.	52	4	Fam. phys.	+51	50	Thyroidectomy	+5	51
35280	F.	52	3	Fam. phys.	+30	25	Thyroidectomy	+6	24
35351	F.	35	2	Quack remedy	+26	14	Thyroidectomy	+3	20
35267	F.	37	3	Internist	+40	23	Thyroidectomy	+6	22
36687	F.	38	4	Fam. phys.	+28	8	Thyroidectomy	+5	20
36589	F.	28	3	Fam. phys.	+28	10	Thyroidectomy	+5	13
38914	F.	22	3	Fam. phys.	+30	10	Thyroidectomy	+6	10
40173	F.	47	2½	Fam. phys.	+52	13	Thyroidectomy	+10	25
39915	F.	45	3	Fam. phys.	+55	13	Thyroidectomy	+0	10
42044	M.	64	3	Quack remedy	+67	51	Thyroidectomy	+8	42
42282	F.	38	4	Fam. Phys.	Too sick	53	Thyroidectomy	Died	
42959	F.	49	4½	Fam. phys.	+62	35	Medical	Died	
31596	F.	18	2	Fam. phys.	+22	10	Thyroidectomy	+10	8
39042	F.	27	8	Quack remedy	+47	13	Thyroidectomy	+2	13
35280	F.	52	3	Physician	+30	25	Thyroidectomy	...	27
39419	F.	30	2	Druggist	None	5	Medical		
39882	F.	30	12	Physician	+40	0	Thyroidectomy	0	15
41177	F.	41	1	Physician	+20	10	Thyroidectomy	+3	10
41288	F.	39	2	Physician	+25	0	Thyroidectomy	-3	5
40064	F.	49	1	Physician	+18	18	Thyroidectomy	-8	30
30262	F.	27	2	Relative	+57	16	Thyroidectomy		
41412	F.	14	3	Physician	+24	10	Thyroidectomy	0	16
27035	F.	36	3	Physician	+24	6	Thyroidectomy	+7	5
41278	F.	25	4	Physician	+28	8	Thyroidectomy	+4	6
40586	F.	14	3	Quack remedy	+46	20	Thyroidectomy	+11	25
31596	F.	16	8	My own	+21	6	Medical	+5	6

The significance of these hyperplastic areas in only three of the specimens examined is not sufficient to warrant considering them pathognomonic of iodine hyperthyroidism. Their importance in toxic adenomas has not yet been explained.

If there is any change in the histological structure of the thyroid gland in cases of iodine hyperthyroidism, it is not evident from a study of these cases. There was nothing to distinguish the gross or microscopical appearance of the gland from either a toxic or a nontoxic adenomatous goiter.

The adenomas are enveloped in a thick capsule of fibrous connective tissue. Microscopically, these nodules are seen to be made up of irregular alveoli of various sizes, lined with flat cuboid epithelium. Some of the alveoli are filled with colloid. The alveoli may be closely packed together, presenting a picture of pressure atrophy, or separated by considerable stroma.

While the pathological picture of iodine hyperthyroidism in no way differs from that of the nontoxic or toxic adenomatous type of goiter, it is of course markedly different from either the purely colloid and exophthalmic forms. The typical, beefy, meaty appearance of the latter type, with its alveoli composed of epithelial hyperplasia without colloid, is in marked contrast to the soft translucent appearance of colloid goiter, whose acini are distended with colloid.

Probably this type of hyperthyroidism can best be accounted for on a physiological basis. Since it has apparently been impossible to explain on a pathological basis, it may be concluded that there is a disturbance in the iodine metabolism. Crotti asserts that the gland in these cases contains a lesser amount of iodine than the normal thyroid or any other form of goiter. This much we know, that iodine hyperthyroidism is concerned only with the adenomatous type of goiter, and does not occur in the purely colloid type.

I believe that adenomas develop in a colloid goiter as a form of compensatory hypertrophy. When the thyroid gland becomes overworked and can no longer supply the body cells with the thyroxine they demand it deposits an incomplete product in the form of colloid, which gives rise to so-called adolescent goiter. In a further effort to supply the demands of the body the thyroid gland is stimulated to form new cells which give rise to adenomatous tissue. Consequently, when iodine is administered in small amounts to children whose thyroids contain small adenomas and a large amount of normal tissue the embarrassment of the gland may be relieved, and thus the tendency of the gland to multiply and form new adenomatous tissue may for a time be checked. When iodine is given in too large amounts to children, or when it is prescribed for adults in whom the amount of normal thyroid is decreased through the degenerative action of the adenomatous tissue, the iodine metabolism of the gland is disorganized. Instead of taking up iodine and

converting it into thyroxin to supply the demands of the body cells, the thyroid is apparently unable properly to metabolize the iodine which is in circulation either in excessive amounts or as an incomplete toxic product.

That there are numerous other views that might serve to explain this phenomenon is evident. Until the pathologists are able to explain to us the various pictures seen in simple adenomas, toxic and exophthalmic goiter, as well as in iodine hyperthyroidism, the true explanation of these conditions will be obscure. Even the etiology of the adenomatous type of goiter is a matter of conjecture. Crile and others maintain that the adenoma does not arise as a form of compensatory hypertrophy in a neglected colloid goiter, but, rather, from a fetal rest. Probably studies in physiological chemistry, such as Kendall's brilliant work, will bring us close to the real solution of these problems.

Conclusions. The number of cases of iodine hyperthyroidism has greatly increased, due to the popular demand for iodine in the treatment of goiter.

In the series of 38 cases reported in this article 20 were observed within the past six months. Two cases terminated fatally.

This condition had generally been termed *iodine-Basedow* in the literature, and consequently has been confused with exophthalmic goiter.

Iodine should not be distributed promiscuously either in water or salt, but should be administered in exact amounts and under a physician's order.

Even minute amounts of iodine are sufficient to initiate symptoms of hyperthyroidism in certain persons with adenomatous goiters.

Iodine should be administered with particular care to children with adenomatous goiters; it should never be given to adults with this condition.

Every child in the goiter belt between the ages of ten and twenty years should receive small weekly doses of iodine for the prevention or treatment of colloid goiter.

Iodine hyperthyroidism is rare in persons under thirty years of age. It develops only in the presence of an adenomatous goiter. The clinical syndrome may be clearly distinguished from that seen in toxic adenoma or exophthalmic goiter. Thrills, bruits and exophthalmos do not occur.

If an early diagnosis is made medical treatment may abort the toxic symptoms. Thyroidectomy is indicated when the condition does not yield to medical measures.

The pathological picture is not characteristic. Grossly, the gland has the typical appearance of an adenomatous goiter containing degenerated, cystic, fibrous and calcareous encapsulated nodules. Colloid may be seen in large amounts. The microscopical picture shows acini of variable size, lined with flat, cuboid cells, and filled

with colloid. Fetal acini and occasional small areas of hypertrophic cells are found.

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REVIEWS.

A PRACTICE OF GYNECOLOGY. By HENRY JELLETT, M.D., F.R.C.P.I., Consulting Obstetrician to the Department of Health of New Zealand; Consulting Gynecologist, Rotunda Hospital, Dublin; Ex-Master, Rotunda Hospital. Fifth edition. Pp. 726; 417 illustrations (many in color) and 15 colored plates. Philadelphia: Lea & Febiger, 1925. Price, \$8.50.

ALWAYS an excellent text for student and practitioner, clear and concise in its diction, well illustrated and reflecting strongly the sound surgical principles and technical ingenuity of the author, this edition maintains its previous standing as one of the best single-volume treatises on gynecology.

The revision includes ample discussion of the work of Sampson on implantation adenomata; of Rubin's gas inflation of the Fallopian tubes; Novak's writings on menstruation; ovarian transplantation; the newer ideas regarding sterility; roentgenotherapy and vaccine treatment have been rewritten. The chapters on surgical principles and technic are up to date, with excellent correlation of the illustrations.

P. W.

LABORATORY DIAGNOSTIC METHODS. A Manual for Physicians, Medical Students, and Laboratory Technicians; by JOHN A. KOLMER, Professor of Pathology and Bacteriology in the Graduate School of Medicine of the University of Pennsylvania and Pathologist to the Medico-Chirurgical and Polyclinic Hospitals, and FRED. BOERNER, Associate in Bacteriology in the Graduate School of Medicine of the University of Pennsylvania. Pp. 338; no illustrations. New York: D. Appleton & Co., 1925.

THIS manual presents in an outline form brief directions in the technic of the various laboratory tests. It includes sections on Clinical Pathology, Bacteriology, Serology, and Blood Chemistry. The first section represents a revision of the Manual on Clinical Pathology by Pepper and Kolmer issued twelve years ago. This is the most helpful section since the methods lend themselves

best to the style of presentation used. The methods described are essentially those employed in clinical pathology, bacteriology, and serology in the Department of Pathology and Bacteriology of the Graduate School of Medicine in the University of Pennsylvania and its Medico-Chirurgical and Polyclinic Hospitals. The book unfortunately contains some typographical errors, which unless recognized by the experienced, would tend to impair the results of such tests as the macroscopic agglutination of antigens of *B. typhosus*, and the complement-fixation test in tuberculosis.

J. S.

MANSON'S TROPICAL DISEASES. Edited by PHILIP H. MANSON-BAHR, D.S.O., M.A., M.D., D.T.M. and H. (CANTAB.), F.R.C.P. (LOND.), Physician to the Hospital for Tropical Diseases, London, and the Albert Dock Hospital; Lecturer at the London School of Hygiene and Tropical Medicine. Eighth edition. Pp. 895; 453 illustrations. New York: William Wood & Co., 1925. Price, \$11.00.

SINCE the publication of the seventh edition of this work tropical medicine has had to deplore the death of one of its foremost pioneers, Sir Patrick Manson, the original author of this textbook. It needs no introduction to the profession, since it has been for a generation the *vade-mecum* of practitioners in the tropics. Under the capable guidance of Dr. Philip H. Manson-Bahr, the book has been thoroughly revised and brought abreast of the latest developments in this field. The subject matter is clearly yet concisely stated, keeping in mind the original plan of the volume that it be adequate in information yet of a handy size to meet the exigencies of travel and of tropical life. The book is well and profusely illustrated. May its career in the future be as illustrious as it has been in the past.

R. K.

DISEASES AND DEFORMITIES OF THE FOOT. By JOHN JOSEPH NUTT, B.L., M.D., F.A.C.S., Professor of Orthopedic Surgery, Polyclinic Medical School and Hospital; Surgeon-in-Chief, New York State Orthopedic Hospital for Children; Orthopedic Surgeon, Willard Parker Hospital, Nyack Hospital and Rockland County Hospital; Member of the American Orthopedic Association. Second edition. Pp. 309; 105 illustrations. New York: E. B. Treat & Co., 1925.

THIS book is not intended as a textbook, but for practical advice to the general practitioner for information concerning the care of the diseases and deformities of the foot. The author gives splen-

did description of the more common conditions and acceptable forms of modern treatment. The opening chapters present excellent study of the anatomy and physiology followed by the method of examination. Such subjects as Schaffer's foot, weak foot, flat foot, club foot, Pott's paraplegia, cerebral paralysis and infantile paralysis are interestingly described with the various forms of treatment and a brief description of the operations for the deformities following these conditions. The text is excellently illustrated.

D. W.

THE EFFECTS OF IONS IN COLLOIDAL SYSTEMS. By DR. LEONOR MICHAELIS, University of Berlin, at present Professor of Biochemistry at the Aichi Medical University in Nagoya, Japan. Pp. 108. Baltimore: Williams & Wilkins Co., 1925.

THIS monograph is a compilation of the material presented by the author in his lectures in this country last year. The origin and behavior of electrical fields surrounding colloidal particles are treated from a theoretical standpoint, emphasis being laid upon the effect of dissolved salts in the liquid phase. These studies are a closer approach to a true knowledge of such phenomena as agglutination, adsorption at cell surfaces and many others, and therefore exert a strong influence on modern biologic research.

B. O.

PHYSICAL DIAGNOSIS OF DISEASES OF THE CHEST. By JOSEPH H. PRATT, A.M., M.D., and GEORGE E. BUSHNELL, PH.D., M.D. Pp. 522; 166 illustrations. Philadelphia: W. B. Saunders Company, 1925.

THAT the authors have made a praiseworthy attempt to produce a book on physical diagnosis of diseases of the chest based on physical laws and pathology is easily recognized in this book; but their effort has only been partially successful. There are two parts to the book, one on the lungs, the other on the heart, and to be fair the reviewer should deal with each separately. The former is far less satisfactory than the latter. There is no subject which requires more careful and lucid writing than the description of physical signs and the details of physical diagnosis. In this respect Part I of the book is much at fault. Furthermore, in a scientific work such statements as the following are, to say the least, dangerous and misleading: One page 159, in a discussion of asthma, "Because the patients of the second class do not respond to cutaneous sensitization tests it does not necessarily follow that the condition of their lungs is not in some measure due to or aggravated by the

elimination, by way of the respiratory passages, of food poisons which gouty or arthritic subjects are not able to dispose of otherwise." Or on page 224, "All old persons likewise become more or less tuberculous, or more accurately, the universal tuberculization manifests itself more distinctly in the old than in younger persons." Nor would one expect such a complete acceptance of "arthritis" as the cause of pulmonary hemorrhage, "if the hemorrhage was due to arthritis the bronchi will soon be found to be absolutely dry." For the medical student the statement that if the supraclavicular gland or glands be found enlarged the presumption is that the enlargement is due to tuberculosis also seems of very doubtful value.

Part II of the book is excellently written and not open to the criticisms which apply to Part I. If bound separately it would be a very valuable book for practitioner or student, but it suffers from being mated with Part I and the book as a whole cannot be recommended for any purpose.

Nor do the publishers escape all criticism. Misprints on pages 12 and 19 and a frequent failure of type alignment deserve mention. Illustrations are numerous, but the vast majority of them are not original and almost a half are taken from German sources, some with the old-fashioned Latin markings, others with German abbreviations. One might at least hope by this time we would be spared an illustration of the old Riva-Rocci sphygmomanometer. The book's heart is good but its lungs are sadly deficient and its prognosis must therefore be very serious.

PROCEEDINGS OF THE INTERNATIONAL CONFERENCE ON HEALTH PROBLEMS IN TROPICAL AMERICA. Held at Kingston, Jamaica, B. W. I., July 22 to August 1, 1924, by invitation of the Medical Department, United Fruit Company. Pp. 1010; 61 illustrations. Boston: United Fruit Company, 1924.

To any one interested in tropical medicine this volume will be of the greatest interest. The seventy papers which it includes touch practically every phase of tropical medicine, and represent the thought of acknowledged leaders in this field. R. K.

MODERN SURGERY. By JOHN CHALMERS DA COSTA, M.D., LL.D., F.A.C.S. Pp. 1483; 1200 illustrations. Philadelphia: W. B. Saunders Company, 1925.

THIS is the ninth edition of this work and a perusal of the publisher's page shows revisions and reprints too numerous to mention.

The above sentence is the best recommendation with regard to the value of this most excellent surgery. Anyone at all familiar with surgery anywhere in the world recognizes the value of any work produced by the author.

The book is up to the minute as regards surgical matters, written in a pleasing style, concise, to the point and good for reference for surgeons, practitioners and students.

I can heartily recommend it as being an extremely good one-volume surgery. E. E.

LUMBAR PUNCTURE. By MARTIN PAPPENHEIM, M.D., Professor at the University of Vienna; Medical Superintendent of the Neurological Department, Municipal Infirmary, Vienna. Translated by GEORGE CAFFEY. Pp. 248; 9 illustrations. New York: William Wood & Co., 1925. Price, \$5.00.

THIS book offers an exhaustive presentation of lumbar puncture, beginning with its history and including its technic, diagnostic value and therapeutic applications. The various methods of investigation applied to the cerebrospinal fluid are described in detail. There is a short appendix on encephalography and puncture of the cisterna. The book is well written and the translation is in the main well done. The technic of cisterna puncture, however, might have been more clearly described, perhaps with the aid of an illustration. R. K.

RECOVERY RECORD (FOR USE IN TUBERCULOSIS). By GERALD B. WEBB, M.D., Consulting Physician, Cragmor, Glockner and Sunnyrest Sanatoria; President, Colorado School of Tuberculosis; and CHARLES T. RYDER, M.D., Cragmor and Glockner Sanatoria; Colorado School of Tuberculosis. Second edition. Pp. 81; 106 temperature charts. New York City: Paul B. Hoeber, Inc., 1925.

To daily temperature blanks is prefixed an excellent outline of the essentials of treatment and the hazards and hopes of the "cure." Many and apt quotations incite to a widening knowledge of the limitations tuberculosis imposes, and to a philosophy which will make the handicap tolerable. Mental rest is properly emphasized. The tone is hopeful. The high mortality is, we think, best driven home by personal talks, adapted to the individual, but always unequivocal. F. McP.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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The Relation of Infection to Diabetic Coma.—In this report by GEORGE GRAHAM (*Quart. Jour. Med.*, 1925, 18, 294) nothing new is brought out in reference to the etiology of diabetic coma, but there is stressed a point which is frequently overlooked in the management of patients suffering from diabetes who go into coma without any apparent cause. The factor that is responsible for the development of the acidosis, leading to coma in patients who have been satisfactorily progressing under insulin therapy, is in the great majority of cases some infection. This infection at times is perfectly obvious but in a certain number of cases it is only found with difficulty. To illustrate his thesis Graham mentions 9 patients with coma. In 2 of the patients no infection could be found; in 2 the infection was plain; in 2 of the patients there was no obvious infection on admission but in whom a definite lesion would have been found at an autopsy if the patient had died in coma; and in 3 there was no sign of any other infection and who "would probably have shown no lesions of other disease at an autopsy if the patient had died in coma, unless the examination had been very complete." Under this last caption is included a case of infection of the antrum of Highmore, a case of mild influenza and one of otitis media. In diabetics with a general or local infection, insulin is much less effective in lowering the blood sugar than when the individual is infection-free and is much more likely to go into coma. The hypothesis that seems most satisfactory to the author to explain this phenomenon is that during infection there is an increased demand for insulin because of the increase in the metabolism.

SURGERY

UNDER THE CHARGE OF

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Symptoms Observed in Nontraumatic Diaphragmatic Hernia.—HEALY (*Am. Jour. Roentgenol*, 1925, 13, 266) noted that the most constant symptom was substernal pain with regurgitation when in the supine position. The next in order is the vague gastric distress, sometimes with tenderness referable to the right upper quadrant and not in the epigastric region, accompanied at times by pain radiating to the back similar to a gall stone attack. Then came vomiting in the morning with hyperacidity. Dyspnea, with palpitation of the heart, was not so common. Only in a very few cases did the author note difficulty in swallowing. Nontraumatic diaphragmatic hernia of the fundus of the stomach is much more common than formerly thought. It is extremely important to make early diagnosis, especially of the smaller type of diaphragmatic hernia, on account of the misleading symptoms which might be the cause of needless operations, also the danger of incarceration with its high mortality. The roentgenologist can help determine the type of treatment by observing the size of the hernia, the symptoms when the hernial sac is filled and the amount of dilatation of the esophagus. He can also suggest the site of operation whether above or below the diaphragm, by determining the position of the diaphragm, the width of the angle at the ensiform and the extent of ossification seen in the costochondral cartilage.

Cancer Infection.—OCHSNER (*Surg., Gynec. and Obst.*, 1925, 40, 335) states that cancer in the beginning always appears as a circumscribed growth. While in this stage it positively can be cured permanently if a sufficient amount of the surrounding tissue is taken out, to insure the total removal of cancer. At first cancer increases by invading the surrounding tissues. Later metastases are formed by the transportation of infected cells from the original growth to distant parts of the body, through the lymph channels of the blood. For a time these infected cells may be interrupted in their journey by intervening lymph nodes. The removal of the original growth, together with all of the infected lymph nodes may still result in a permanent cure. This can be accomplished with greater certainty if the removal is carried out with cautery. The incidence of cancer is greatest in persons above middle age. It is practically confined to persons living in civilized communities. Domestic animals living in civilized communities also become infected with cancer. Wild animals are free from it. Cancer rarely occurs in skin covered by clothing. Filth

applied either externally or internally influences the occurrence. Clean skins are rarely the seat of cancer, as shown in the case of Japanese who take daily hot baths. Persons eating vegetables grown in soil fertilized with human excrement suffer largely from cancer of stomach and colon. The natives of the tropics and the arctic regions are equally free from cancer. These two classes live on food not contaminated with manure or human excrement. The actual cause of cancer has not been established to the satisfaction of all who are entitled to an opinion. Heredity seems to have a definite relation to the development of cancer in that it at least provides a predisposition or lack of immunity. Cancer in plants has been proved to be due to the *Bacillus tumefaciens*, by Erwin F. Smith, of the United States Laboratory of Plant Pathology. John Nuzum has isolated a filterable micrococcus from many cancers in man and in animals. The same micrococcus has been isolated from cancer produced artificially.

The Early Diagnosis of Cancer of the Large Bowel.—HOMANS (*Boston Med. and Surg. Jour.*, 1925, 192, 695) declares that nothing could well be more harmful to progress in the treatment of cancer than the belief that strictly internal cancers can seldom, if ever, be identified early enough in their course to be cured by surgery. Constipation, associated with well established colic and distention, is a late symptom of cancer and patients who have reached this stage would be rarely cured, if it were not for the well known tendency of adenocarcinoma of the colon to metastasize late. It is a moderate or intermittent constipation, associated perhaps with indigestion and discomfort, which is under particular consideration in this condition. In the right side of the colon, symptoms suggestive of subacute appendicitis, tending to appear in attacks in which the constitutional and local signs are less marked than the patient's sensations suggest. There is possibly local soreness or distention of the bowel and quite probably since tumors in this region are often cellular and bleed easily, a noticeable degree of anemia. In the transverse colon there are attacks of low abdominal cramps or colic, sometimes associated with vomiting and in a majority of instances some degree of constipation. Not infrequently there is freedom from constipation and discomfort between attacks. In the descending colon and sigmoid flexure, there are either of two types of symptoms—a type marked by mild attacks of gaseous discomfort and low abdominal cramps, sometimes but not necessarily associated with a moderate degree of constipation and another type marked by steadily increasing constipation ending in obstruction. In the rectosigmoid there are symptoms similar to those due to obstruction in the sigmoid proper, but tending evermore to constipation and to the presence of blood upon the stools.

A General Survey of Radiotherapy in Malignant Disease.—SCOTT (*Brit. Med. Jour.* 1925, 1, 596) says that the primary growth is but an indication that the patient has malignant disease and does not by any means give a correct idea of its extent. To insure the plan of attack being developed on sound lines, it must be based on the assumption that malignant disease is a generalized disease and not a local lesion. The author maintains that if primary growth can be destroyed by radiation,

metastases will be equally susceptible, possibly to a much smaller dose for they are usually less bulky. Some radiologists advocate the high, others the low voltage technic. A better distinction would be homogeneous and heterogeneous radiation. Homogeneous radiation (high voltage) means the use of a bundle of rays of one particular penetration. Heterogeneous (low voltage) means the use of a large number of rays of all penetrations, filtering out those rays likely to injure the skin. It is important that the heterogeneous radiation be utilized. It has its limitations, but the newer method should be an addition and not a substitute. Radiation does not destroy or remove unwanted cells like the cautery or knife. Profound changes are set up, which allow them to be absorbed or replaced by healthy cells. This is important, for it means that malignant cells can be made to undergo a change, resulting in their replacement by normal tissues without necrosis taking place—in short a metamorphosis without cellular death. It is thus evident that there is a local indirect effect of radiation. Carried further is it not possible to create it on a larger scale generally, calling up all nature's forces to assist in the cure? The work of many physicists supports this theory.

The Relative Merits of the Various Treatments of Peptic Ulcer.—

BALFOUR (*Minn. Med.*, 1925, 8, 218) believes that the methods which are worthy of discussion include both medical and surgical procedures. The surgical procedures of unquestioned merit are excision alone, excision with gastroduodenostomy, gastroenterostomy with or without excision and partial gastrectomy. The indications for medical treatment depend largely on the situation of the lesion. In chronic gastric ulcer prolonged medical treatment is justified only when surgery is absolutely contraindicated, because of the age or the condition of the patient. The more familiar one becomes with the uninterrupted course of chronic gastric ulcer, which is one of progressive disability, the more certain one becomes of the fact that prolonged medical treatment is never justified if the patient is fit for operation. In cases of chronic duodenal ulcer, such serious objections to medical treatment do not exist since the symptoms are usually not so severe, the disability so great, nor the danger of fatal complications so marked as in cases of gastric ulcer. It is generally recognized that the fundamental principle in the successful treatment of gastric ulcer is the removal of the ulcer whenever feasible. For small accessible ulcers, local excision by cautery or knife, combined with gastroenterostomy gives excellent immediate and late results and the procedure is usually safe and simple. For larger ulcers partial gastrectomy is the operation of choice since it cannot be determined whether or not such ulcers are malignant and it is well established that all chronic gastric ulcers are potentially malignant. In the surgical treatment of chronic duodenal ulcers, one fact stands out that no one operation will give perfect results. Four procedures are considered in the article: Gastroenterostomy, with or without excision of the ulcer, pyloroplasty or gastroduodenostomy with or without excision, excision alone and partial gastrectomy. To attain the best results from gastroenterostomy a safe principle to follow is that the more extensive the lesion, the more definite the indication.

PEDIATRICS

UNDER THE CHARGE OF

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Mumps of the Pancreas.—STEVENS (*Arch. Pediat.*, 1925, 42, 333) reports 4 cases of mumps involving the pancreas. An analysis of his cases showed that all 4 were in boys, and their ages ranged from six to almost thirteen years. The onset was rather sudden, after doing well, on the fifth or sixth day of the infection. The first symptom noted was rising temperature. The fever rose from nearly normal to 102° or more and was sustained at the high level for the period of active symptoms, which lasted from one and a half to two and a half days. The highest recorded temperature was 104°. The pulse was rapid and proportionate to the temperature. Pain was generally of mild character at the onset, and was referred to a point just below the ensiform. It was described as of a steady, aching character. Abdominal cramps in 2 cases may have been caused by liberal catharsis given at home to cure the pain. Tenderness in the epigastrium was a constant sign. Pressure to elicit this sign usually brought on a wave of intense nausea. It was not possible to make out the presence of a mass with any certainty. This tenderness in the epigastrium persisted for several days after the temperature returned to normal. Vomiting was an outstanding symptom, coming on within a few hours and persisting for two days with total intolerance for food. Half of the cases could retain sips of water only. In the more severe cases the repeated retching brought up bile-stained fluid on the second day. The prostration was out of proportion to the degree of pain complained of. There was no true shock, although general weakness is to be expected after continued vomiting. Constipation was the rule. The shortest period of active symptoms was a day and a half and the longest period was two and a half days. The condition terminated by a rapid fall of the temperature to normal and with a cessation of nausea. There were two inconstant symptoms. Icterus of a mild grade was noted in 2 cases. This may have been secondary to the bilious vomit and reabsorption. In another case conjunctival hemorrhages occurred, presumably from the severe retching. The author thinks that this condition is a metastasis to the pancreas of the virus causing mumps. He feels that the great danger lies in wrongly diagnosing this condition as an acute surgical process. He thinks that the symptoms are very suggestive of appendicitis, intussusception and ileus. In the presence of a parotitis the diagnosis lies in favor of the pancreatic mumps.

Difficulties in Diagnosis of Acute Phase of Epidemic Encephalitis in Children.—HALLIDAY (*Lancet*, 1925, 1, 763) points out that the diseases most liable to be confused are gastroenteritis, tuberculous meningitis and pneumonia. He emphasizes the fact that examination

of the cerebrospinal fluid will always exclude meningitis, and in certain instances will establish a diagnosis of encephalitis. In gastroenteritis the gastrointestinal symptoms are often overlooked on account of others suggesting a disease of the nervous system, such as headache, delirium, drowsiness, sighing respirations and pseudoptosis. Pneumonia in its early stages before the development of physical signs in the chest may be mistaken for encephalitis when it is ushered in by convulsions, delirium, twitchings, meningism, drowsiness, vomiting and pain in the side. On the other hand, pain in the side, a cough and rapid respirations may be the first symptoms of encephalitis.

Congenital Cardiac Defect in Children.—MACGREGOR (*Edinburgh Med. Jour.*, 1925, 32, 251) reports an interesting case which showed some unusual features. There was an absence of the right auriculo-ventricular orifice. There were also defects in the interauricular and interventricular septa. The heart was greatly enlarged. Both atria were markedly dilated and communicated freely with each other through the foramen ovale which was widely patent. There was no communications between the right atrium and the right ventricle, the right auriculoventricular orifice and the tricuspid valve being entirely absent. There was thus no outlet for blood from the right atrium except through the foramen ovale. The pulmonary artery arose from it in the usual position, and it possessed a perfectly normal valve, and was of the usual caliber. The left auriculoventricular orifice was somewhat wider than usual, but was in the natural position, and possessed a valve with two cusps, exactly resembling a normal mitral valve. The aorta was normal in every way as was also its valve. The ductus arteriosus was patent, but very narrow and seemed to be in the process of becoming obliterated. In the interventricular septum there were two apertures. The larger, which readily admitted the forefinger, was situated in the upper part of the septum, immediately below the aortic valve, and communicated with the infundibular portion of the right ventricle. The other, which was barely half as large, was situated near the apex, the two openings being separated from each other by a thick band of muscular substance. No cardiac defect was suspected in this case until the day of death, which occurred when the patient was seven weeks of age.

Pneumonia in Children.—ENGEL (*Berlin. klin. Wchnschr.*, 1925, 4, 681) found invariably in the paravertebral lobular pneumonia of infants a tendency for the posterior portion of the right upper lobe, and to a less extent of the center of the lower lobe to become involved. This seems to be due to a relative atelectasis of these parts. The chest of an infant is not capable of much distention, and is practically in the inspiration position. The air can be increased, therefore, only by tachypnea, not by deeper respiration. The imprints of the ribs, or the intercostal bulgings of the lungs, were quite pronounced in infants that were dyspneic. This phenomenon and the typical localization of the pneumonia becomes rarer after the first year. The diffuse lobular pneumonia in infants causes surprisingly slight physical symptoms in spite of the gravity of the condition. Lobar pneumonia affected the right upper lobe in 27 and the left lower lobe in 3 of the

30 cases less than twelve months of age. This tendency is evident in the first three years of life. It may be due partly to the same mechanical factors which cause the localization of the paravertebral dystelectatic pneumonia. The left upper lobe that usually remains free has its regional lymph nodes outside of the lungs, in the mediastinum along Botalli's duct and the arch of the aorta, and not in the hilum. The summer peak of mortality of children from gastrointestinal diseases has been superseded by the winter and spring peak from respiratory infections. Scarlet fever and diphtheria kill fewer children than the pneumonia complicating measles and whooping cough.

Tetany as a Cause of Convulsions in Very Young Infants.—POWERS (*Jour. Am. Med. Assn.*, 1925, 84, 1907) reports a case. When first seen a number of possibilities were suggested and considered. Many of these were eliminated or considered as highly improbable on general clinical grounds. Of this number infantile tetany was one. This proved to be the correct diagnosis. It was strongly suggested by the electrical reactions, but was definitely established by the finding of the blood calcium concentration of 5.93 mg. per 100 cc of serum. The highly favorable response to treatment with calcium chlorid, cod-liver oil and direct sunlight would offer confirmation of the diagnosis. Several points in the history and symptomatology presented by the infant were in evidence against the diagnosis of infantile tetany. Until the electrical reactions were determined there was no point in favor of this diagnosis. The history gave a statement of a prolonged labor with face presentation, and this was highly suggestive of a birth hemorrhage as the cause of the convulsions. The convulsions were largely limited to the right side. While the convulsions attributed to birth injury may be and usually are generalized, the presence of predominantly unilateral attacks were especially suggestive of an injury in the nature of a cerebral hemorrhage. The patient showed none of the characteristic symptoms and signs of tetany. There was no laryngeal spasm, no tenseness of the facial muscles, no Chvostek's sign and no carpopedal spasm. While local twitchings occur frequently in manifest tetany, frank convulsions are rarely predominantly unilateral as in this case. The fact that as demonstrated by this case the only clinical manifestation of tetany may be convulsions should be borne in mind. Another point to be remembered is that tetany may develop in a very young infant, this patient being only five weeks of age when the symptoms were manifested. Another point is the possibility of congenital tetany just as there is a possibility for congenital rickets.

The Heart in Diphtheria.—MARVIN (*Am. Jour. Dis. Child.*, 1925, 29, 433) made an electrocardiographic and clinical study of 90 patients with diphtheria. The only abnormalities in the electrocardiographs were disturbances in the auriculoventricular or the intraventricular conduction. Sinus arrhythmia occurred invariably in young patients with heart rates below 95 per cent. Auricular and ventricular premature beats, sinoauricular block and variations in the form of the P-wave were noted seldom and appeared to have no significance. No evidence was obtained to indicate that in some patients the heart was primarily injured and in some others the peripheral circulation suf-

ferred the first and greatest damage. In patients with circulatory impairment the picture seemed to be that of myocardial failure. The signs of myocardial involvement which appeared to be of the greatest value were vomiting, hepatic engorgement and a change in the first heart sound. Syncope occurred but once and gallop rhythm was noted only three times. There was a complaint of abdominal pain in 5 of the 13 fatal cases. Necropsy in 5 cases revealed widespread myocarditis. In 1 case the entire conduction system was profoundly damaged, in 1 the sinoauricular node was alone affected and in the others the conduction system seemed normal. The vagus nerves were found to be normal in the 1 case in which an examination was made. The electrocardiographs prove of great value in diagnosis and prognosis.

GYNECOLOGY

UNDER THE CHARGE OF

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AND

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The Use of Radium in Uterine Cancer.—At present radium is little used in the treatment of cancer of the uterine fundus because the results of operation in this disease have been quite satisfactory. GRAVES (*Am. Jour. Obst. and Gynec.*, 1925, 9, 445) goes a bit further and warns that carcinoma of the fundus is a distinct contraindication to the use of radium because he has shown that early cancer of the fundus that is entirely curable by operation is liable to recur when treated by radium alone. This uncertain curability by radium is sufficient to condemn its use, but there is still another reason which should convince the most enthusiastic of radiologists. It has long been a matter of observation that cancer of the fundus metastasizes first in the ovaries. The mode of transmission of the disease from the endometrium to the inner tissues of the ovary was a scientific mystery until the epochal work of Sampson taught us the frequency with which endometrial elements may become transplanted into the ovarian substance. The intrauterine application of radium will not destroy endometrial elements in the ovaries, so that the treatment of cancer of the fundus should be by radical operation that includes both ovaries. In regard to *cancer of the cervix*, the author reminds us that before the advent of radium the extended Wertheim operation had reached the limit of its possibilities and progress depended solely on the improvement in skill of the individual operator. Radium has given new hope in treating this dreadful and rapidly increasing disease. In its use as a palliative, the author believes that there is almost no case so far advanced in which the distressing discharges and often the pain may

not be alleviated by irradiation. In less advanced but still incurable cases the disease may, with few exceptions, be checked by a single treatment, so that the patient may live from one to four years in perfect health. When recurrence does take place it is apt to be internal and unassociated with the offensive discharges and fistulæ that were formerly universal in the final stages. Though not a few surgeons have discarded operation altogether in the treatment of *operable* cervical cancer in favor of radium, he has not yet come to a final conclusion. At first convinced that it was the duty of the surgeon to operate upon every operable case instead of taking the more comfortable path of irradiation, he has latterly made certain concessions to the radiologists. For example, he has greatly modified his classification of cases. He has changed the term "operability" to "curability by operation," which has quite a different significance. Whereas formerly over a period of many years in the author's clinic they operated upon about 60 per cent of all cases, they now subject to operation only about 20 per cent. During the last five or six years they have carried on parallel series of operated and irradiated cases, in which the disease is limited to the cervix and frankly curable either by operation or radium. Such patients have been chosen for irradiation as, on account of obesity or constitutional weaknesses, incurred a special risk in operation. Sufficient time has not elapsed to draw authoritative conclusions from this series, especially as the operated cases greatly exceed the others in number. Nevertheless a recent comparison of the two types of cases of less than five years' duration shows a similarity of results that has been surprising to the author and encouragingly favorable to the use of radium.

Movable Kidney.—In summarizing his experiences in the treatment of movable kidney, MATHÉ (*Surg., Gynec. and Obst.*, 1925, 40, 605) states that the great majority of movable kidneys cause no symptoms and require no treatment. In a certain percentage of cases, however, renal mobility forms a definite clinical entity characterized by lumbar pain, urinary, gastrointestinal and nervous disturbances, loss of weight, etc., and requires fixation by abdominal support or surgical intervention. The condition is more common in the female because the renal fossæ are shallower, cylindrical or even funnel-shaped, being wider below than above. This predisposition to displacement is increased at puberty because of the widening of the bony pelvis. Its greater frequency on the right side is due to the shape of the renal fossa, the presence of the liver on that side and the weaker support afforded by the less well-developed right perirenal fascia. The majority of cases of renal ptosis can be relieved by the proper abdominal support, fattening and strengthening exercises. On the other hand, Mathé says that nephropexy is a justifiable operation. It has been employed by numerous urologists of note who have found it satisfactory. It relieves symptoms and is indicated in the following cases of movable kidney: (a) When the belt fails or is poorly tolerated; (b) in those cases complicated by ureteral kink caused by fibrous bands; (c) when the sag of the kidney has caused the ureter to kink over an aberrant vessel; (d) in those cases in which adhesions have developed around a prolapsed kidney holding it in place; (e) in chronic colon pyelitis when faulty

drainage due to increased mobility is not corrected by the belt. He has employed nephropexy with success in 96 per cent of the 30 cases operated on. Of those 46 per cent had obtained no relief from mechanical supports. He believes that surgical suspension of the kidney has fallen into disrepute not on account of its inefficacy, but because it has been performed when it has not been indicated, the technic has been faulty or there has been failure to realize the necessity of exposing the ureter and relieving any condition which might be present, which unrelieved, would defeat the purpose of the operation.

Blood-sedimentation Test.—According to the experiences of BAER and REIS (*Surg., Gynec. and Obst.*, 1925, 40, 691), the blood-sedimentation test is useful in determining the presence or absence of infection in the body. With pelvic pathology a negative sedimentation test (a sedimentation time over two hours) conclusively rules out pelvic infection. The rate of sedimentation is directly proportional to the virulence of the infection and the test is a further aid in determining the safe time for operation in cases of pelvic inflammatory disease, and they believe that this test seems a more delicate prognostic index, good or bad, than either the leukocyte or temperature curve. The sedimentation time, or rate, is the number of minutes required for the red blood cells to separate from the plasma of citrated blood. Many methods and types of tubes for making such determinations have been devised. The technic of Linzenmeier appears to the authors to be the most reliable, the most accurate and also the simplest of all methods that have been suggested, and it was therefore used by them in this study. The tubes used are of hard glass, 5 mm. in diameter and 6.5 cm. in length and have a capacity of more than 1 cc. They are marked at the 1-cc point and also at 6, 12, 18 and 24 mm. below this mark. The tubes as well as the syringe with which the blood is drawn from one of the superficial veins at the elbow, must be perfectly clean and dry. Two-tenths cubic centimeter of a 5 per cent sodium citrate solution is drawn into the syringe and then 0.8 cc of blood. This is shaken until mixed and then placed in one of the tubes and allowed to stand at room temperature. The blood mixture level must be exactly at the 1-cc mark. The time is taken when the mixture is placed in the tube and again when the line of demarcation between the erythrocytes and the plasma reaches the 18-mm. mark; a millimeter reading is also taken at the end of one hour. This latter reading has been recently recommended as being more comparable than the number of minutes required for the line of demarcation to reach the 18-mm. mark and besides much time can be saved in specimens requiring several hours for complete sedimentation. The sodium citrate solution must be comparatively fresh and the tubes must be kept vertical, for slanting the tubes increases the rate appreciably. If the blood clots before being well mixed with the citrate solution the test is valueless. There are many theories to explain the reason for this blood phenomenon but no definite conclusions have been reached.

Ectopic Muellerianoma.—In a certain percentage of women the process of menstruation is abnormal, inasmuch as part of the menstrual blood finds its way into the Fallopian tubes and escapes into the pelvic

cavity, carrying with it either endometrial epithelium and stroma cells or Fallopian tube epithelium. These elements are deposited upon the surfaces of the various pelvic organs, and in a certain percentage of instances become embedded and grow into them. They proliferate actively and menstruate concurrently with the uterine endometrium. Our knowledge of this subject is largely due to the original work of Sampson which we have repeatedly quoted in the past. This subject has attracted the attention of BAILEY (*Jour. Obst. and Gynec., Brit. Emp.*, 1924, 31, 539), who has presented a rather extensive review of the life history of these "chocolate" cysts. He states that misplaced Fallopian tube epithelium also reacts definitely to menstruation, but in a lesser degree than uterine epithelium and it is less invasive than the endometrial cells. These abnormally situated epithelial elements penetrate into the tissues of the affected organs—the ovary apparently being best suited for their activities—and eventually produce in them tumor formations and excavated cavities containing the products of their menstrual activity. Many names have been applied to these tumors, such as ovarian hematoma, ectopic adenoma, adenomyoma and endometrioma, but no one of these names can thoroughly embrace both the endometrial and Fallopian tube types of this extrauterine pelvic tumor, and therefore the author suggests the name of "ectopic muellerianoma," which is expressive of both types of the disease, since the abnormally situated elements in each case are of Muellerian origin. These tumors are only locally malignant and do not tend to form metastases.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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Further Statistics on Chlorin Gas as a Treatment for Respiratory Diseases.—JONES AND GAROFALO (*Arch. Otolaryngol.*, 1925, 1, 58) reported the results of about 800 chlorin-gas treatments administered to 220 individuals, suffering from acute, subacute and chronic inflammatory processes of the respiratory tract, hay fever, asthma or suspected tuberculosis. The technic of treatment and the dilution of the chlorin gas used (0.02 mg. per liter) was that recommended by Vedder and Sawyer in their original report (*Jour. Am. Med. Assn.*, 1924, 82, 764) of the chlorin treatment. Treatments were given only once in some instances and in others were repeated at intervals of twenty-four hours for several days. There was an improvement in the acute cases involving the upper respiratory tract, as indicated by shrinking of the mucous membrane, diminution of discharge, relief of irritation and freer breathing—all of which beginning immediately after the treatment but lasting only a few hours. Extension of the inflammation into the lungs and trachea was not perceptibly influenced.

The authors state that in "Asthmatic patients, allergic and tuberculous patients chlorin treatment is contraindicated." The chlorinated air did not alleviate freely suppurative conditions of the rhinopharynx. Although their number of cases was small, it was felt that whooping cough did not respond to the treatment. In the dilution tolerated chlorin was not sufficiently germicidal to act as a sterilizing agent for operations on the nose and throat. In 106 treatments, where the bacteriologic findings were compared with the clinical results, there was an agreement in 67 cases (65.1 per cent) and disagreement in 39 cases (34.9 per cent).

Bacteriologic Study of the Nasopharynx in Patients Treated with Chlorin Inhalations.—In a companion article, PATTERSON (*Arch. Otolaryngol.*, 1925, 1, 64) gave the findings of bacteriologic studies of the nasopharynx on the same individuals treated with chlorin gas inhalations. The technic consisted in culturing the nasopharynx by means of the West tube and planting on rabbits' blood-agar plates. The cultures were taken before entering the chlorin room and five minutes after the treatment had terminated. At the end of twenty-four hours' incubation the number of colonies of those plates seeded from the persons before treatment was compared with those after treatment. The colonies, as observed forty-eight hours after inoculation, were classified as green, hemolytic, staphylococcus-like and diphtheroid. In a total number of 184 tests the growth on the after-treatment plate was less in eighty-eight instances, or 48 per cent of the total. In 43 instances, or 24 per cent, the after treatment plate showed more growth than the control. In 53 instances, or 28 per cent, there was no obvious difference. Of the various types of microorganisms the author felt that the results indicated that hemolytic streptococci and diphtheroid bacilli were affected most. Blood-agar plates inoculated with pure cultures of some common pharyngeal bacteria, and then exposed in an atmosphere containing 0.015 mg. chlorin per liter for various intervals up to one hundred and twenty minutes, showed very little or no effect of the gas on the subsequent development of the bacteria, except in plates exposed for more than ninety minutes. A chlorin concentration of 0.02 mg. per liter of air gave a distinctly more appreciable reduction in the bacteria of the nasopharyngeal mucus in the patients, and exhibited a greater inhibitory effect on the plate cultures. The bacteria suspended in the air itself appeared to be very largely destroyed by the chlorin. From her investigations the author concludes that "Sterilization of the respiratory mucous membrane by inhalation of chlorin in a concentration of 0.015 to 0.02 mg. per liter of air for an hour or two is not to be expected;" that "The concentrations of chlorin used do exert an effect, however, and often this may be in the direction of microbe reduction, of possible assistance to the body defenses in combating superficial infection;" and that "Although chlorin inhalation is not without possibility of injury, its extensive application to acute superficial respiratory inflammations, under suitable scientific control, appears justified in the light of the laboratory studies. The ultimate decision as to its value must be based on extensive clinical trial."

Value of Chlorin in the Treatment of Colds.—Realizing the importance of controlled observations, DIEHL (*Jour. Am. Med. Assn.*, 1925, 84, 1629) subjected 425 university students to chlorin gas in a concentration of from 0.015 to 0.0175 mg., and compared the results with those observed on 392 students who received medical treatment for their acute respiratory diseases. By means of a questionnaire, sent to the patients at the end of a week, the results of the chlorin inhalations were ascertained. Of the total that were treated with chlorin, 51.4 per cent reported themselves cured within three days, while 47.9 per cent of those given medical treatment recovered in the same time, showing practically no difference. There was still less difference between the percentages that recovered under chlorin and medical treatments during the first week, 73.3 and 72.6 per cent, respectively. However, the percentage of cures within the first day was consistently higher with chlorin than with medical treatment. This difference was most marked when the colds were treated within the first three days, but the percentage of cures with chlorin was also higher for colds treated after the third day and for the total number treated. The beneficial effects of chlorin evidently were experienced within the first day after the treatment, because each day after the first the percentage of recoveries was higher from medical treatment than from chlorin. The chlorin treatment was apparently more beneficial in acute rhinitis than in any other type of acute cold. The author confirms the observations of others that persons subject to asthma suffered ill effects from the chlorin inhalations. The results of the treatment of whooping cough were somewhat encouraging, but not conclusive.

New Method of Demonstrating the Labyrinth of the Inner Ear in Situ.—After a macerated temporal bone has been thoroughly cleaned, degreased, bleached and dried, the empty spaces of the labyrinth, seventh nerve and mastoid cells, etc., were filled with Wood's metal through the internal auditory meatus, according to Siebenmann's method. FREEDMAN (*Bull. Internat. Assn., Med. Museum*, 1925, 11, 33) then decalcified the superficial bony tissue by immersing in a solution of 5 per cent nitric acid for about two days. When the temporal bone was sufficiently decalcified, so as to render cutting it with a scalpel easy, the superior semicircular canal was denuded. By following the posterior limb backward the posterior semicircular canal, embedded in the posterior part and running parallel with the posterior surface of the petrous portion of the temporal bone, was encountered. By drilling in the enclosed angle between the superior and posterior canals the horizontal canal was found. Lateral to the arch of the horizontal canal occurred the antrum filled with Wood's metal, which was whittled away, exposing the arch of the horizontal canal and the horizontal portion of the facial nerve beneath it. With very little dissection through the external auditory meatus the cap of bone of the promontory was lifted up, exposing the rounded basal turn of the cochlea. Removal of the roof and anterior surface of the internal auditory meatus brought to light the seventh and eighth nerves. The white metallic semicircular canals and cochlea were painted green and the nerves the conventional yellow. The author concludes that "A temporal bone prepared in this fashion in conjunction with

the corrosion method of Siebenmann, and the usual method of exposing the hollow semicircular canals and cochlea in the dry bone, form an almost indispensable 'triad' for the proper orientation of the labyrinth of the inner ear and its relation to the seventh nerve, both for the student and ear specialist."

RADIOLOGY

UNDER THE CHARGE OF

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The Differential Diagnosis of Certain Chronic Lung Lesions.—In roentgenologic diagnosis of lung lesions, accuracy depends upon the interpreter's knowledge of the lung anatomy and pathology, according to FRANK S. BISSELL (*Am. Jour. Roentgenol. and Rad. Ther.*, 1925, 13, 2). Tuberculosis is most commonly an aërogenic infection and its earliest lesions occur in the area of Chauvet, and also anteriorly in the second and third interspaces near the periphery. A healed and an active lesion may exist in opposite lungs; primary basal tuberculosis is very rare, and its differential diagnosis cannot be made roentgenologically. Tuberculous pleurisy is almost always associated with tuberculosis of the lung. It is usually possible to make a roentgenologic differentiation between a cavity and a simple abscess by searching other parts of the lung fields for the more characteristic evidence of tuberculosis. In tuberculous infection there is a marked tendency to early involvement of the lung parenchyma, often restricted for the time to one or more primary lobules, taking on a pyramidal shape with the base toward the periphery, and is usually in the upper-lung fields. In the chronic bronchopneumonia of streptococcic origin the process is almost invariably unilateral and usually confined to one of the lower lobes.

Final Results in the Treatment of Carcinoma of the Uterine Cervix at Radiumhemmet, Stockholm.—In a report on 505 cases of primarily radium treated carcinoma of the cervix, within the period 1914–1921, JAMES HEYMAN (*Am. Jour. Roentgenol. and Rad. Ther.*, 1925, 13, 2) demonstrates very encouraging results. The technic used, as elaborated by Forssell, is a small number (usually 3) of intensive treatments (each 105 to 112 mg. radium element) with strong filtration (equivalent to 3 to 4 mm. lead), given in the course of three to four weeks. At first only inoperable cases were treated, but following a report in 1919–1920 by the author that 33.3 per cent of his cases were alive four to five years after treatment of inoperable cases, operable cases were also sent to the "Radiumhemmet." Of 505 cases, one-third were forty-five years of age or less, one-third forty-six to fifty-five years and one-third over fifty-six years of age. In 217 cases treated, 20.29 per cent were symptom free five years after the commencement of treatment. The

author has noted that any variation from a definite plan of treatment affects the end result; that repeated removal of tissue during treatment is very dangerous; that the average result of radium treatment on operable and borderline cases is on a par or better than results obtained by surgery; that the primary mortality is very small with radium; that this treatment has great developmental possibilities; and that for uniform results a very exacting technic should be followed closely.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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The Present Status of the Malarial Inoculation Treatment for General Paresis.—Since Wagner V. Jauregg introduced the malarial inoculation treatment of paretic neurosyphilis much work has been done in different countries and many favorable results have been reported. In this article LEWIS (*Jour. Nerv. and Ment. Dis.*, 1925, 61) reports the results obtained in the treatment of 68 patients at St. Elizabeth's Hospital, Washington. Nine patients failed to develop malaria and 8 of those who did respond could not be followed up because they left the hospital. In 16 patients "complete remissions" occurred. In 19 others the disease was arrested. Twelve progressed to extreme deterioration and 13 died either during or shortly after treatment. The author discusses the following points: (1) In the selection of cases paresis must be diagnosed and differentiated by at least two of three objectives (mental, physical and serologic) one of which must be the serologic picture. The vascular type of neurosyphilis should be ruled out. (2) Some of the most notable remissions have occurred in late cases in which syphilitic aortitis was perhaps present. (3) Written permission for the treatment should be obtained as it is not without some danger. (4) The absence of quinin idiosyncrasy should be determined before treatment is begun. (5) Malarial blood must be kept at 37° C., and must not be shaken lest the plasmodia perish. (6) Intramuscular injection is as good as the intravenous method. The blood must show only the pure tertian type of malaria. (7) Inoculation malaria responds well to quinin treatment. (8) Many paretics do not develop malaria upon inoculation. (9) Malaria itself probably is a factor in certain deaths occurring with this treatment. (10) Muhlen's scheme of treatment gives the best results in the interruption of the malaria. (11) Reviewing the results of a number of investigators the author considers these to depend essentially upon the stage of the disease, the earlier the more certain the remission. The maximum results are not obtained at once. Permanency of improvement cannot be determined until sufficient time has elapsed. (12) Reese and Peter's observations on blood and spinal fluid, particularly in that there is no

parallelism between clinical improvement and spinal fluid changes, are confirmed. (13) Objective improvements are striking. (14) Regarding the beneficial action of malaria the author believes: (a) There can be no specific reaction; (b) the rise in temperature is not alone responsible; (c) Mueller's concept of a vasodilation in the brain should be seriously considered. Changes in vascular tonus occur in various parts of the body following injection. The abdominal vasodilation is quickly neutralized by the unimpaired vasoconstrictors but the same dilation in the local inflammatory areas in the brain is of longer standing. If this should be found to be true a follow-up specific therapy is perhaps indicated. The results obtained are strikingly better than those gained by any other method. A conscientious investigation of the phenomenon produced is indicated.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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The Differentiation of the Paratyphoid-enteritidis Group—With a view to obtaining some conception of host specialization of paratyphoid-enteritidis bacilli from mammalian sources (other than human) an exhaustive study has been made by EDWIN O. JORDAN (*Jour. Infect. Dis.*, 1925, 36, 309). The report consists of a thorough review of the existing data and an examination of over one hundred strains of paratyphoid-enteritidis bacilli from widely distributed sources. In connection with the former, exact classification is difficult by reason of incomplete observations of strains in numerous instances by those reporting them. Confusion in classification has arisen because certain German writers insist on classing *B. paratyphosus* B with *B. suipestifer*, while English bacteriologists identify *B. suipestifer* with the so-called Aerttrycke strains. The author concludes that *B. paratyphosus* A is apparently an exclusively human strain. He has found no authentic instance recorded of natural animal infection with this type. In the horse a specialized member of the group, *B. abortivo-equinus*, predominates, and he believes it to be the only organism in the group producing natural infection in equines. It is serologically distinct from all other members of the group. Culturally it may be distinguished by the following characteristics: (1) *B. paratyphosus* B shows rapid arabinose fermentation, rapid dulcitol fermentation, trehalose fermentation, while (2) *B. suipestifer* shows no blackening lead acetate, no inositol fermentation. This strain has never been found in infections of other animals. In rodents (chiefly mice, rats, guinea pigs and rabbits) two types are found: *B. enteritidis*, most commonly

in laboratory rats (sometimes in mice); the other type in rodents, particularly guinea pigs, is the *B. paratyphosus B. aertrycke* type. The proportion of the two is not known. In pigs 38 out of 50 cultures were culturally and serologically of the *B. suipestifer* type. The only other strain of this type of animal origin was from a monkey. No strain has been encountered from rodent or bovine sources. On the remaining 12 of the 50 strains 10 were *B. paratyphosus B.*, all true Schottmüller, and two other types have been found in swine, *B. enteritidis* and *B. voldagsen* (*B. paratyphosus C?*). Bovine strains are usually *B. enteritidis* or *B. paratyphosus B. aertrycke* type. The few sheep strains studied are all *B. paratyphosus B. aertrycke* type. Thus it will be seen that host specialization has occurred to a considerable extent in man (*B. paratyphosus A.*), horse (*B. abortivo-equinus*) and pig (*B. suipestifer*). The relation of *B. paratyphosus B. aertrycke*, to rodents is not so marked. *B. paratyphosus B.* (Schottmüller) is found in human paratyphoid fever almost as often as *B. paratyphosus A.*, but unlike the latter it is also found in swine. The most cosmopolitan member of the group is *B. enteritidis*, found in human, porcine, bovine and rodent infections.

"Hormone" Medium.—A modification of Huntoon's "hormone" media is described by BAILEY (*Jour. Infect. Dis.*, 1925, 36, 340). The author claims that the media retains all the qualities of other "hormone" media, with the added advantages of being clearer, less expensive and even richer in "hormone" content than the others. The egg is omitted as being unnecessary for purposes of filtration, and it is suggested that it may even be a source of stubborn contamination. Special reference is made to the preparation of "hormone" blood agar and its value for preserving pneumococci and streptococci. Sixty-two out of 68 cultures of pneumococcus and all of 32 cultures of streptococcus were kept alive on this medium for twelve months without transplantations.

Phagocytosis of Erythrocytes in the Bone Marrow with Special Reference to Pernicious Anemia.—PEABODY and BROUN (*Am. Jour. Path.*, 1925, 1, 169) precede a report of an investigation of the phagocytosis of red blood cells in the bone marrow by clasmotocytes (Sabin) with a survey of the present knowledge of this subject. For control observations 4 specimens were studied of normal vertebral bone marrow (from patients dying from trauma) and 130 specimens of vertebral bone marrow from patients dying as a result of a great variety of conditions. The basis of the paper is a study of 11 cases of pernicious anemia, 10 of which died during an acute phase of the disease and 1 during a remission. Excellent results were obtained for study by fixing the smears from the bone marrow or from emulsions of bone marrow in salt solution, in Zenker's solution, and then staining. The stains used were eosin and methylene blue or one of the Romanowsky stains. Neutral red and Janus green are also recommended. They conclude that phagocytosis of erythrocytes occurs to a very limited extent in normal marrow, though it may be considerably increased by a variety of pathological conditions, notable among which are certain cases of cirrhosis of the liver and of infectious diseases, such as pneumonia, typhoid fever and tuberculosis. On the other hand, in the

active stages of pernicious anemia it occurs to a degree which, with rare exceptions, is not met with in other diseases, and during a remission it may cease to be a prominent factor in the bone marrow. The ingested cells, furthermore, do not appear to be foreign cells that have been introduced by transfusion. Views are presented on the reason and process of the phagocytosis and on whether or not it is an incident in the disease or a significant phase in its pathology. It is suggested that phagocytosis of erythrocytes may be a factor in the production of the hemolytic jaundice and of the anemia in pernicious anemia.

The Combined Microscopic Demonstration of Glycogen and Lipoids.

—The demonstration of glycogen and lipoids in the same preparation offers difficulty because these two substances possess very different solubilities. The method which has previously been in use, and has been modified by various authors, consists of a combination of the best carmine staining along with the use of osmic acid. This method has not been entirely satisfactory inasmuch as the osmic acid treatment leads to variable results, and the reduction of osmic acid is brought about mainly by oleic acid while the remaining fatty substances are unaffected. ARNDT (*Centralbl. f. allg. Path.*, 1925, 35, 545) suggests using a 10 per cent solution of formalin saturated with dextrose for the fixation of the specimens. The material is then cut on the freezing microtome and subsequently handled either in saturated solutions of dextrose or in 70 per cent alcohol. The author made use of solutions of chlorophyl for the staining of the fatty substances, hematoxylin for the staining of the nuclei and levulose for the mounting of the sections. The regular Best method for staining glycogen was found satisfactory. He claims to have been able to obtain very good results for the dual demonstration of fat and glycogen, and states that the method is important for the study of the tissue changes which arise when these two substances make their appearance in different organs in disease. In certain tissues he was able to demonstrate the presence of both of these substances within the same cell.

Primary Tumors of the Ureter.—Primary tumors of the ureters are quite unusual. The most common variety that has been found is the one arising from the epithelial lining of the tube and resembling a tumor similar in origin to that found in the pelvis of the kidney. A few cases of mixed tumor have also appeared in the literature and the still rare tumors of smooth muscle origin have been described. DJENG-YAN KU (*Centralbl. f. allg. Path.*, 1925, 35, 549) reports a case of myosarcoma arising in a man, aged seventy-five years, which had been growing slowly until it involved the entire circumference of the lower portion of the ureter and then spread into the surrounding tissues. This tumor, late in its development, brought about a constriction of the ureter with a secondary hydronephrosis. The author was able to determine that the tumor was composed of muscle tissue containing numerous giant cells. The tumor was intimately attached to the muscle layer of the ureter and, although its malignant qualities were not evident in all its portions, it showed active mitoses in certain parts and an invasive quality in the neighboring structures. The neighbor-

ing connective tissues showed a peculiar hyalin degeneration not unlike amyloid. The author suggests that the tumor is of congenital origin, inasmuch as he also found multiple lipomata in the neighborhood of the tumor and bone formation in both lungs.

Variations in Specificity and Virulence of Pneumococci during Growth in Vitro.—Using a strain of Type I pneumococcus, REIMANN (*Jour. Exper. Med.*, 1925, 61, 587) has studied the variations induced in the organism by growth in artificial media, and has attempted to correlate these differences. Plain bouillon was used as a medium, to which were added varying concentrations of bile or homologous or heterologous immune serum. The bacteria were adapted by successive transfers to the presence of the bile in the medium. Blood agar was used for detecting colony differences, and the test for the immunological specificity was made by the so-called thread reaction. In certain cases it was found advisable to work with single cells, an interesting method for the isolation of which is reported. After the culture had been transferred 240 times in broth observations were made. Colonies were found to resolve themselves into rough (R) and smooth (S). The S strain remained type specific for Type I serum, but the R strain clumped in all three sera. Furthermore the S strain produced a specific soluble substance for the precipitin reaction while the R failed to do so. Similarly the S strain retained its virulence for white mice while the R did not do so. Both strains coagulated milk and fermented inulin and only the S strain showed a capsule. Growth in bile media produced similar changes, successive transfers finally eliminating the S strain. The same findings resulted from using a medium containing 1 per cent Type I antipneumococcus serum. Animal passage eliminated the R forms. S and R forms could be separated by growing the bacteria in heterologous serum. The work throughout indicated that the S form can be readily changed to the R, but that the reverse change is not probable, the whole trend of pneumococcus cultures being toward a decrease in virulence and a loss of type specificity. The changes in individual bacteria appear to be abrupt. Clearly written details of the experiments are given.

Experimental Pneumonia in Mice following the Inhalation of Streptococcus Hemolyticus and of Friedländer's Bacillus.—STILMAN and BRANCH (*Jour. Exper. Med.*, 1925, 41, 623) report a study of a series of mice exposed to fine bacterial mists of pneumococcus, Streptococcus hemolyticus and Bacillus friedländer in enclosed chambers, infection taking place by inhalation. All mice were autopsied, cultures taken from lungs and heart's blood and the number noted showing pneumonia with or without consolidation. A very small percentage of normal mice exposed to pneumococci died but this percentage greatly increased in animals alcoholized. A total of 1001 mice were exposed to the pneumococcus—216 to Streptococcus hemolyticus and 169 to Bacillus friedländer. In the case of the pneumococcus the organisms rapidly disappeared from the lungs and only an occasional mouse succumbed to pneumococcus septicemia. Upon alcoholization a large percentage died within five days of exposure. In using Streptococcus hemolyticus and Bacillus friedländer the organisms could be recovered

from the lung and blood for a number of days after exposure, and a large number died of septicemia during thirty days after spraying. The longer the organisms persisted in the lungs, the more certain the fatal issue. In another paper the same authors (*Jour. Exper. Med.*, 1925, 41, 631) give details of the pathology of the experimental pneumonias above described. Sections fixed in Zenker's were stained with eosin and methylene blue and modified Gram's stain. Twenty-eight pneumonia lesions in 80 mice were studied, all of which showed the organism concerned present in lungs and blood. The initial lesion in all seemed to be a polymorphonuclear infiltration of the interstitial tissue. In pneumonias occurring spontaneously in stock mice the lesion is usually a mononuclear response. In the early stages the three types can only be differentiated bacteriologically. Later they assume individual pathological characters. The result of the study would indicate that the term "broncho" may not be aptly applied to the lesions, but that "interstitial," "lobular" and "lobar" would be more expressive. The experimental pneumonias seemed, according to the authors, to be of the nature of a cellulitis of the lung, with the initial lesions in the lower respiratory tract, around the bronchioles, atriæ and alveoli. An indifferent plate illustrates the second paper.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Eight Weeks' Quinin Treatment for Malaria.—GRIFFITHS (*Pub. Health Rept.*, 1925, 40, 538) tried quinin for the purpose of malaria control from the public health point of view, with results which were not very satisfactory, as shown by the following conclusions: (1) Under arrangements as satisfactory as could be made for having the eight weeks' quinin treatment for malaria taken by rural people as represented by the group herein considered, it was not practicable to get the entire treatment taken as recommended. (2) Sufficient effect from quinin was secured to prevent frank manifestation of malaria in 90.6 per cent of the persons treated, but in 25.4 per cent of the group parasites were found on examination of thick smears after the supervisory treatment, and before sufficient time had elapsed for new infections to show in the blood; in the group of 74 people treated, 36.5 per cent were positive on blood examination before treatment; after the

treatment 25.4 per cent showed parasites, a reduction of only 11.1 per cent. (3) In a heavily infected, poorly-nourished population, with a probable high rate of hookworm disease the quinin treatment, as taken, failed to free a large percentage of cases of either asexual or sexual forms of the parasites, but did prevent to a great degree the development of paroxysms. (4) From the last week of August to the second week of November, during which time, no supervisory quinin treatment was given, the increase of infections, as shown by examination of thick blood smears, was 46.6 per cent, the great increase being due largely to the number of infections by *P. falciparum*. (5) If the late season infections were newly acquired infections the transmission occurred through a relatively small number of vectors with an increasingly high number of gametocyte carriers toward the end of the season.

Vaccination by Mouth Against Bacillary Dysentery.—ENLows (*Pub. Health Rept.*, 1925, 40, 639) reviews previous work on the subject and presents experiments of her own, and the following summary and conclusions: (1) It is pointed out that the method of vaccination by mouth is not new; it was used more than nineteen years ago in an effort to produce immunity to the Shiga type of bacillary dysentery; renewed interest in the problem followed Besredka's experiments, in which he introduced the use of beef bile as an erosive agent, preparing the way for the entrance of the subsequently ingested bacilli into the deeper lying cells of the mucosa which he considered responsible for the local immunity. (2) A brief review of some of the early work is given, and also of the work done since Besredka's experiments, including a few of the experiments (foreign) on man; these experiments are somewhat contradictory in that at least a part of the animal experiments do not seem to confirm the work of Besredka, while all of the human experiments favor this method of vaccination; the human experiments are, however, too few in number to warrant definite conclusions. (3) The author's experiments with rabbits show that the greatest protection (70 per cent) was afforded by the subcutaneous method, but that a fair degree of protection (57 per cent) resulted from the vaccination by mouth, and that there was much less danger involved in the use of the latter method; beef bile is shown not to be necessary in vaccinating by mouth against the Shiga type of bacillary dysentery. While the method of vaccinating by mouth against the Shiga type of bacillary dysentery should still be considered in the experimental stage, two facts are evident: (1) The danger and discomfort are too great to recommend the use of the subcutaneous method of vaccination against the Shiga type of infection. (2) Since vaccines can be so prepared that no danger nor discomfort follows their ingestion, and since at least some immunity is shown to follow such procedure, vaccination by mouth is apparently worthy of further trial.

The Incidence of Illness in a General Population Group.—SYDENSTRICKER (*U. S. Pub. Health Rep.*, 1925, 40, 279) states that a true picture of ill health, and, therefore, of the problems to be attacked by those who are engaged in preventing disease, is not adequately portrayed by death statistics. The obvious reason for this is that mortality records by definition do not include the cases of illness that are not

fatal, to say nothing of the suffering and the lowered vigor and the lessened efficiency among the living. A study of illness in a general population group in a typical small city not only shows the inadequacy of mortality statistics for this purpose but suggests the kind of picture that complete morbidity records would afford. Looking at it in broad outline only, it was found in the group of persons studied that: (1) Over 100 cases of illness occur annually for each death. (2) More than half of the morbidity was due to respiratory diseases. The ratio of respiratory illnesses to deaths from respiratory causes was more than 300 to 1. (3) Diseases and disorders of the digestive system caused an annual illness rate of 117 per 1,000 but a mortality rate of less than 1 per 1000, a ratio of about 200 to 1. (4) The "general diseases"—epidemic and non-epidemic—composed principally of those diseases against which public health effort has been mainly directed, caused only 11 per cent of all illnesses. (5) While deaths occur principally in infancy and in old age, ill health, as measured by the incidence of illness, occurs with comparatively little variation throughout life. It is prevalent among the young, those in the "prime of life," and the aged without much discrimination. This picture inevitably suggests a point of attack upon the causes of ill health not adequately recognized now—the diseases which are incident between the extremes of life. If, as it is now the custom, success of public-health work is to be measured in money terms, surely no more cogent argument could be put forward than that of the economy of preventing loss of the efficiency of the population at those ages when health means the most in production. It is not hard to figure that a day of sickness prevented at the age of thirty or forty years is more profitable than at the age of seventy years. But, in a broader sense, the diseases which cause ill health are a challenge to the sanitarian, not merely because they have an exhausting effect upon man's power to resist death but because they lessen his ability to achieve and his capacity to enjoy life in the years of his most abundant strength.

The Rickettsiæ and their Relationship to Disease.—WOLBACH (*Jour. Am. Med. Assn.*, 1924, 84, 723) states that the term "rickettsia" should be applied only to microorganisms adapted to arthropods ("insects") and pathogenic for vertebrates and having the following characteristics: Small size, pleomorphism, slight affinity for anilin dyes and intracellular habitat in the arthropod host. It should be kept in mind that practically nothing is known about the nonpathogenic, rickettsia-like, intracellular microorganisms of arachnids and insects, whether casually present or in the role of symbionts. The work so far done in this field has been superficial and evasive of the main problems concerning relationships between microorganisms and hosts; it has, however, served to obscure the status of the pathogenic rickettsiæ. The *Dermacentroxenus rickettsi* is the cause of Rocky Mountain spotted fever, and that *Rickettsia prowazeki* is the cause of typhus the author regards as proved. There is strong presumptive evidence that *Rickettsia pediculi* is the cause of trench fever. It is certain that the rickettsiæ represent a new group of microorganisms, and probable that other pathogenic ones will be found.

Developments in the Fields of Mental Testing.—DOLAN (*Pub. Health Rep.*, 1924, 39, 2519–2520) gives the following recapitulation of the data presented in the paper: In summing up the work that has been accomplished in the field of mental testing, mention will be made of only the most salient facts. After the successful application of the Binet-Simon test of general intelligence, interest in this branch of psychology increased. The greatest impetus to the movement came with the advent of war, during which the Army Alpha and Beta tests were organized and successfully applied. Up to the close of the war, work had been done in testing general intelligence only, but the development of the Army tests had opened so many new possibilities that psychologists enthusiastically took up the task of broadening the field and extending its limits. Trade tests and tests rating specific abilities were organized, the number and kinds of general intelligence tests were increased, and, finally, attempts were made to measure temperamental qualities. This process of development laid stress upon the quantity of tests, however, at the expense of their quality. As a result, the real problems of securing accurate measurements were not realized until analyses were made of the quality and reliability of tests already in existence. Then the complexity of mental testing became apparent and the significance of such factors as emotional reactions, correlations, methods of administration, establishment of criteria, and correct analysis were brought to light. Tests as they stand today are by no means perfect as far as the consideration of these factors is concerned. More stress is constantly being laid upon mental testing as an individual problem, and it is by individual testing that the best results are secured, the best not only for the individual but for society. Too much emphasis cannot be placed upon the value of tests in vocational guidance. It is during the school period, when the youth of the country is planning its future, that correct guidance along suitable channels is absolutely essential. It means not only satisfaction and pleasure to the individual, but the utilization of his powers in the field where they are most needed and most valuable. It means satisfaction to the individual, to industry, to society, to the eugenicist, to the race. Thus the effects of mental testing are far-reaching and significant, and embrace not only the field of psychology but the fields of psychiatry and of medicine as well. The mental testing movement is still little more than in its infancy. Many intelligence tests have been standardized as giving accurate measurements of general ability. Accurate measurements may also be secured from certain tests of specific abilities and aptitudes. Tests of temperamental qualities are still more or less unreliable. Research agencies throughout the country are industriously carrying on the work, placing more emphasis upon the quality of their tests and making them more reliable. The problem is by no means simple. Tests are far more complicated when gone into qualitatively than one is likely to realize, for it means delving deeper into hidden traits and workings of the human mind that are not yet fully understood or even realized. But when mental tests are standardized and give measurements that may be relied upon, then, if applied to those boys and girls who are in school or just embarking in the field of industry, foundation will be laid for the most fruitful and far-reaching results.

The Relation of Vegetative Activity of Bacteria to Pathogenicity.—FELTY and BLOOMFIELD (*Jour. Exper. Med.*, 1924, 40, 703) report experiments to show that distinct differences exist between relatively young cultures of bacteria and the same strains during the period of decline as regards invasive power and pathogenicity, and state that these differences must be distinguished clearly from specific alterations in virulence such as those produced by animal passage. The exact interpretation of these observations is not, however, perfectly clear. The authors are inclined to believe that simple alterations in vegetative activity might account for the differences described, but to what extent the results have been due to injury to the bacteria by products of culture growth it is impossible to say, and further work will be necessary to settle this point. The experiments seem to bear definitely on the problem of infection in as far as they show that purely temporary modifications of growth activity whether or not brought about by specific injury lead to changes in invasiveness which are quite analogous to the test-tube phenomenon of lag. It has been previously shown that there exists in the upper air passages a mechanism by means of which foreign particles and bacteria can be eliminated within a few hours. It seems highly likely on the basis of the present work that bacteria entering in an inactive growth phase—for example dried in dust or perhaps from a chronic carrier—may be disposed of before activity can be resumed, whereas organisms introduced in the stage of active growth—as from a case of acute disease—may be able to take advantage of a portal of entry. It is further possible that these experiments may have some bearing on the genesis of epidemics, especially as regards the pre-epidemic phase, and these matters will be discussed at another time.

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ORIGINAL ARTICLES.

ADIPOSITY AND OTHER ETIOLOGIC FACTORS IN DIABETES
MELLITUS.*

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AND

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PHILADELPHIA.

THIS contribution to the etiology, incidence and death-rate of diabetes mellitus, is based principally upon the mortality statistics of Philadelphia for the last forty-five years, and also figures derived from cases of adiposity and diabetes personally observed. It may be fairly assumed that increase in the death-rate indicates an increase in the incidence of diabetes, since it has been conclusively shown by Cabot¹ that the percentage of accuracy of statement in respect to the diagnosis of this disease is high.

It is to be recollected, however, that notwithstanding the earlier detection of glycosuria and the greater frequency of blood-sugar determinations in symptomless cases, as well as closer and more enlightened attention to their dietetic supervision, in recent years the mortality-rate had been, according to the results of our statistical studies, rising steadily until the introduction of insulin as a remedy. This is shown graphically by Chart I (see below) which is based on the mortality figures for Philadelphia for the last forty-five years, or from 1880 to 1924 inclusive.

Tracing (A) shows the rise in the deaths from diabetes mellitus for practically the same period of time for each 100,000 of the population, or from 3.53 per cent to 17.6 per cent, while (B) represents the decline in the death-rate from all causes per 1000 of the popula-

* Read before the Association of American Physicians, May 5, 1925,
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tion of this city during that period, or from 21.14 per cent to 12.95 per cent. Joslin² claims that the patients seen at the present day are older and represent a milder type of the disease, which of itself indicates "not so much new cases as a greater zeal displayed in their discovery." The various agencies that have caused the fall in the general death-rate in Philadelphia and other large cities are too well known to require a detailed statement of the facts connected therewith. Suffice to say that the reduction has been most notable in certain specific instances, for example, the communicable diseases of childhood, infantile complaints and such infectious diseases of adult life as typhoid fever, tuberculosis, malaria and yellow fever.

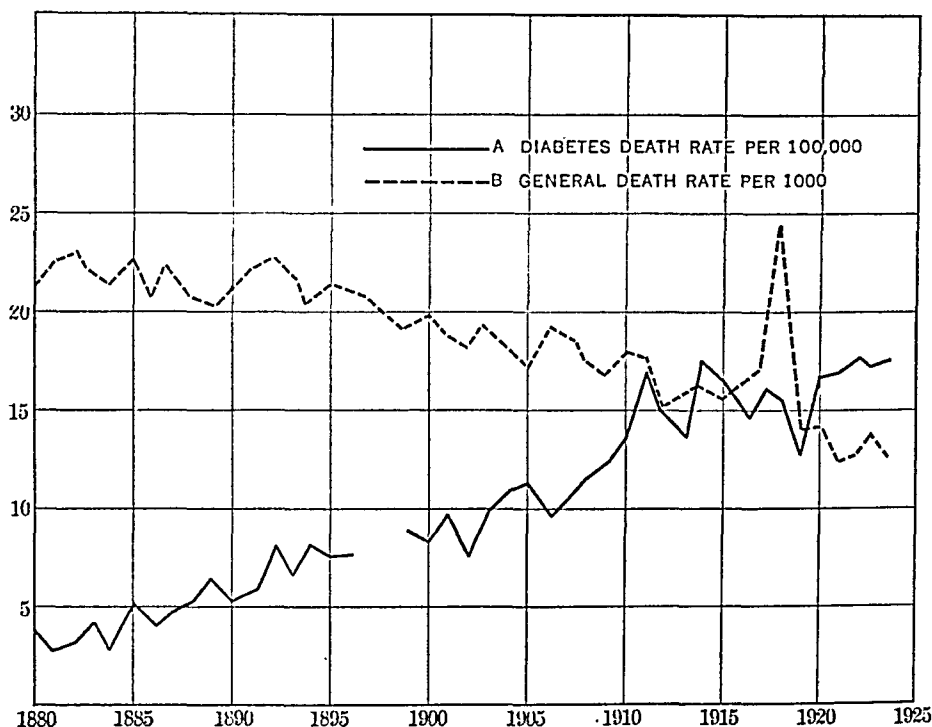


CHART I.—The break in the continuity of tracing (A) is due to the fact that no data were available for the years 1897 and 1898.

Insulin has checked the further rise in the death-rate during the last half of 1923 and during 1924 in Philadelphia (see Chart I). It is claimed by the Metropolitan Life Insurance Company³ that a reduction in the death-rate from diabetes among their industrial policy holders during the last half of 1923 and the first quarter of 1924 as the result of the extensive use of insulin during that period has occurred. As shown by Foster⁴ treatment of diabetic coma with insulin often causes consciousness to return. It is quite probable that the case-mortality percentage of diabetes will be considerably reduced by the widespread and more judicious use of insulin in the future, through an indefinite postponement of the fatal issue and possible cures in functional cases. Admitting the truth

of these statements, the influence of insulin may be disregarded as affecting our mortality-data, covering a period of forty-three years ending with June 30, 1923.

Emerson and Larimore⁵ give as a reason for studying the deaths from this disease "the considerable shift in relative importance numerically of the leading causes of death which has dropped tuberculosis from first to fourth place and has brought diabetes up to tenth place." It is of interest to note here that in the Registration Area of the United States in 1920, diabetes appears in the twelfth place. Similar mortality data for the year 1923 in Philadelphia are presented in Table I. These, it will be noted, also assign diabetes to twelfth place (see Table I).

TABLE I.—RELATIVE RATING OF THE LEADING CAUSES OF DEATH IN PHILADELPHIA (1923).

Disease.	Total.
1. Heart disease	4162
2. Pneumonias (lobar and broncho)	3260
3. Acute and chronic nephritis	2375
4. Cancer	2234
5. Tuberculosis of lungs	1867
6. Congenital debility and malformations	1156
7. Diseases of arteries	813
8. Apoplexy	753
9. Diarrhea and enteritis (under two years)	571
10. Influenza	425
11. Injuries by falls	337
12. Diabetes	335
13. Appendicitis and typhlitis	328
14. Syphilis	323
15. Injuries by automobiles	304
16. Diphtheria	270
17. Embolism and thrombosis	254
18. Measles	223

There has been a decided shift in the numerical rating of diabetes in Philadelphia in recent times; for instance, in 1913, or ten years prior to having reached the twelfth place, it occupied twenty-second place. It is clear that while there was a decided increase in the mortality-rate of diabetes in Philadelphia until 1923, it was not quite as great as in New York City. We may account for New York's higher death-rate by the higher percentage of Jews in that city as compared with Philadelphia. Table II further emphasizes the higher average mortality-rate for New York as compared with Philadelphia.

TABLE II.—AVERAGE DEATH-RATE FROM DIABETES PER 100,000 FOR BOTH PHILADELPHIA AND NEW YORK FOR FORTY-FIVE YEARS ACCORDING TO FIVE YEAR PERIODS.

	1880 to 1884.	1885 to 1889.	1890 to 1894.	1895 to 1899.	1900 to 1904.	1905 to 1909.	1910 to 1914.	1915 to 1919.	1920 to 1924.
Philadelphia	3.4	5.1	6.6	8.0	9.1	11.2	15.5	15.0	17.0
New York	4.1	6.4	8.0	9.8	12.3	14.8	17.0	19.8	21.4

The death-rate of diabetes mellitus in Philadelphia during forty-five years according to age groups and sex is shown in Table III. The steady rise in the mortality-rate among both sexes during many years and especially the phenomenal rise among females during the last fifteen years are shown by both Table No. III and Chart No. II (see below).

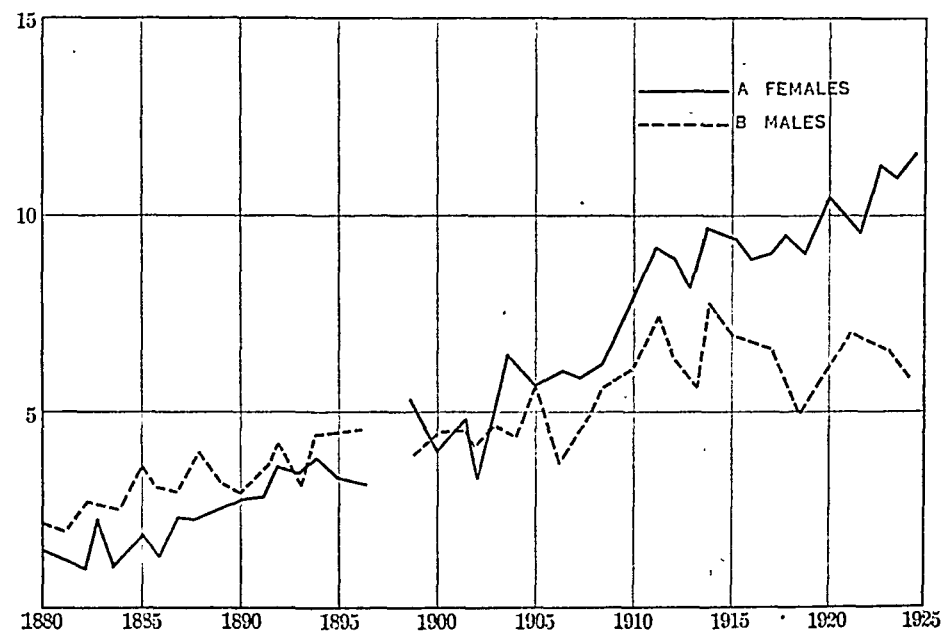


CHART II.—The interruptions in continuity of tracings (A) and (B) are due to the fact that no figures for 1897 and 1898 were available.

Emerson and Larimore found on comparing the experience of the "Registration States and of New York City by five-year-age groups for 1920, that after the age of forty, women show higher diabetes death-rates, except that males in the Registration Area over eighty years of age again take the lead." In New York City, while the proportion of all diabetic deaths has remained about stationary under twenty years of age for upwards of fifty years, the preponderance for that period occurred among the males. While our own collective investigations do not indicate the sex in relation to age groups, they show only a slight increase in the mortality-rate between birth and twenty years of age during forty-five years in Philadelphia.

A glance at Table III will show that the rise in the diabetes death-rate is beyond both the increase in the general population and the total deaths from all causes. Again, the death-rate per 100,000 from this disease was more than five times greater in 1924 than in 1880 in Philadelphia. For example, when the column showing the total diabetes deaths for this city is consulted, it will be seen that the mortality in 1924 exceeded ten times that of 1880, while the population for the former year was only two and a half times that of the latter. The increase in the death-rate and the incidence of

diabetes has been unparalleled by any other affection, if we except severe epidemics, such as the sudden and widespread appearance of malignant influenza and the like.

TABLE III.—DEATHS AND DEATH-RATES, ALL CAUSES, AND FROM DIABETES, FROM 1880 TO 1924.

Year.	Population.	Total deaths all causes.	Crude death-rate per 1000.	Diabetes deaths.			Diabetes death-rate per 100,000.	Percentage diabetes deaths of all deaths.	Age groups.			
				Total.	Male.	Female.			0 to 19.	20 to 39.	40 to 59.	60 +.
1880	848,835	17,942	21.14	30	19	11	3.53	0.167	3	12	6	9
1881	868,814	19,761	22.74	25	15	10	2.88	0.126	9	12		4
1882	888,793	20,293	22.83	28	20	8	3.22	0.137	3	7	8	10
1883	908,772	20,338	22.38	39	21	18	4.29	0.191	4	7	13	15
1884	928,751	20,320	21.88	29	21	8	3.12	0.191	3	8	11	7
1885	948,730	21,694	22.87	48	33	15	5.05	0.221	2	12	16	18
1886	968,709	20,349	21.01	42	31	11	4.33	0.206	3	11	15	13
1887	988,689	22,194	22.45	49	29	20	4.95	0.221	4	8	19	18
1888	1,008,669	20,750	20.57	52	36	16	5.15	0.251	3	11	20	18
1889	1,028,649	21,038	20.45	64	33	31	6.21	0.304	9	13	18	24
1890	1,049,020	22,273	21.23	55	28	27	5.24	0.247	1	14	20	20
1891	1,073,693	24,003	22.36	64	35	29	5.95	0.267	4	10	28	22
1892	1,098,366	25,033	22.79	84	45	39	7.65	0.332	5	14	22	43
1893	1,123,039	24,442	21.76	72	35	37	6.41	0.295	4	15	24	29
1894	1,147,712	23,500	20.48	92	48	44	8.01	0.391	5	18	30	39
1895	1,172,385	24,634	21.01	92	52	40	7.85	0.373	8	17	22	45
1896	1,197,038	24,782	20.70	92	53	39	7.66	0.371	7	7	39	39
1897	1,221,711	23,505	19.24									
1898	1,246,385	24,614	19.75									
1899	1,271,059	24,534	19.30	114	48	66	8.97	0.465	7	22	34	51
1900	1,295,852	25,695	19.83	109	57	52	8.41	0.424	7	15	38	49
1901	1,312,706	24,659	18.66	124	60	64	9.44	0.503	5	25	36	58
1902	1,347,560	24,374	18.09	98	54	44	7.27	0.402	6	12	40	40
1903	1,373,414	26,725	19.46	133	65	68	9.69	0.498	5	23	49	53
1904	1,399,268	25,971	18.56	152	65	87	10.86	0.585	7	17	59	69
1905	1,425,122	24,807	17.41	161	81	80	11.30	0.649	8	16	60	77
1906	1,450,976	27,768	19.14	140	52	88	9.65	0.504	5	17	56	62
1907	1,476,830	27,476	18.61	157	70	87	10.62	0.571	10	28	51	68
1908	1,502,685	25,926	17.25	178	84	94	11.84	0.687	9	23	63	83
1909	1,528,540	25,029	16.37	196	90	106	12.82	0.783	8	19	70	99
1910	1,554,902	27,045	17.39	220	96	124	14.15	0.813	8	26	78	108
1911	1,583,190	27,276	17.23	264	118	146	16.68	0.968	6	23	97	138
1912	1,611,478	24,513	15.21	245	100	145	15.20	0.999	10	25	102	108
1913	1,639,766	25,612	15.62	230	94	136	14.02	0.898	9	18	86	117
1914	1,668,054	26,918	16.14	290	128	162	17.39	1.077	7	41	100	142
1915	1,696,342	26,287	15.50	278	118	160	16.39	1.058	12	21	90	155
1916	1,724,630	27,621	16.02	256	104	152	14.84	0.927	6	27	101	122
1917	1,753,058	29,681	16.93	273	115	158	15.57	0.920	7	39	96	131
1918	1,781,346	42,933	24.10	275	106	169	15.44	0.641	8	30	117	120
1919	1,809,635	25,946	14.34	233	88	145	12.87	0.898	14	26	92	101
1920	1,837,924	26,516	14.43	295	106	189	16.05	1.112	10	32	97	156
1921	1,866,212	23,704	12.70	310	129	181	16.61	1.307	12	35	103	160
1922	1,894,500	25,103	13.25	337	126	211	17.78	1.342	18	29	135	155
1923	1,922,788	26,654	13.86	335	124	211	17.42	1.256	5	35	139	156
1924	1,951,076	25,280	12.95	345	116	229	17.6	1.365	11	26	120	188

The differences between the deaths of the sexes on comparing individual and groups of years are interesting. For example, from 1880 to 1902 the diabetic deaths among males exceeded those among females in Philadelphia with two exceptions, whereas from 1903 until 1924 inclusive the reverse obtained. It will be observed that in recent years the excess of deaths among the females progressively increased until the sex ratio reached nearly 2 to 1 in favor of the latter sex. Emerson and Larimore state that at the ages of forty-five and over for New York, the proportion of all diabetes deaths has increased and those of females at a greater rate than those of males. This statement agrees with the results of our observations for Philadelphia as stated above. The precise causative factors which have brought about the rising death-rate of diabetes during the last half century remain in great measure unknown. It has been shown, however, that in this period of time the food intake has gradually increased and also that the amount used has passed far beyond human needs. Emerson and Larimore give charts and tables which indicate that rises and falls in the sugar consumption "are followed with fair regularity within a few months by similar rises and falls in the death-rates from diabetes, the changes during the period of the World War being particularly striking."

The main purpose of this article is to show the etiological relationship of obesity to diabetes (see Table IV). Many allied questions, however, have arisen in connection with the consideration of this subject and some of these have been statistically investigated and discussed. Fisher and Fisk⁶ have shown definitely, by tables compiled from medico-actuarial statistics of life insurance companies, that the effect of overweight on mortality among healthy individuals is considerable. If this be true, and added to our knowledge of the predisposing causes of diabetes, it would be wisdom on the part of the diabetics to avoid overweight.

Certain generally accepted facts appertaining to predisposition to diabetes have not been given any detailed consideration. The greater hazard of diabetes among the Jews as compared with Gentiles, however, we believe, received further significant confirmation from the results of our studies.

The importance of advancing our knowledge of the predisposing causes of a widely prevalent disease such as diabetes mellitus, can hardly be exaggerated. The statistical inquiry into the predisposing influence of obesity in diabetes mellitus, which we have conducted has been limited exclusively to cases personally observed, or a total of 1306 cases of the former condition, and 145 of the latter. As shown by a glance at Table IV, our studies were established on a few simple lines and the chief results obtained, indicated thereon, are largely self explanatory.

According to our figures, the average percentage of overweight is higher among females than males, and while this is true of both

Gentiles and Jews (see Table IV), the latter race shows the higher average percentage of overweight. It would appear, therefore, that the more marked average adiposity among females, brought about, as has been pointed out, by a larger sugar consumption and more sedentary lives, is the cause of the greater incidence of diabetes in them. It may be a matter of surprise, therefore, that Table IV does not show a preponderance of cases of adiposity among females over males, but only a higher average percentage of overweight as already stated.

TABLE IV.

	Total number of patients.	Total number of obese.	Percentage of obese.	Average percentage of overweight of all obese.	Total number of diabetics.	Percentage of diabetics.	Average percentage of overweight in diabetics.
Gentiles:							
Male . . .	2913	606	20.80	21.84	57	1.96	19.88
Female . . .	2927	488	16.67	27.02	55	1.88	23.20
Total . . .	5840	1094	18.73	25.33	112	1.92	21.62
Jews:							
Male . . .	652	113	17.33	24.55	18	2.91	25.07
Female . . .	598	99	16.56	29.71	15	2.51	31.22
	1250	212	16.96	26.44	33	2.71	27.55

Table V confirms in a striking manner the fact that the incidence of diabetes among obese Jews is higher than among obese Gentiles, the ratio being as 12 to 8 in favor of the former. While "more Gentiles than Jews are underweight and more Jews than Gentiles overweight" (Joslin), the higher incidence among Jews may be dependent solely, as Joslin contends, upon a greater average percentage of overweight as shown by the figures just given. It would appear to us, however, that the difference in the average percentage of overweight is not great enough to account for this discrepancy in incidence. Table V also shows that 26 cases of diabetes occurred in persons not above the normal weight.

TABLE V.

	Gentiles.	Jews.
Total number of obese cases	1094	212
Average percentage overweight	25.33	26.44
Number of diabetics in obese cases	92	27
Percentage of obese cases with diabetes	8.4	12.74
Total diabetics normal or underweight	20	6
Percentage of total diabetics underweight	16.96	18.18
Percentage of totals with diabetes underweight	1.80	2.75

Again, Table VI covers the same points for a twenty-year period, from 1910 to 1924 inclusive and tells much the same story.

TABLE VI.—1910 TO 1924.

	Cases of adiposity.	Male.	Female.	Average per cent of overweights.	
				Male.	Female.
Gentiles . . .	786	451	335	19.98	25.64
Jews . . .	173	96	77	21.78	26.95
Total . . .	959	547	412		

TABLE VII.—1915 TO 1924.

	Cases of adiposity.	Male.	Female.	Average per cent of overweights.	
				Male.	Female.
Gentiles . . .	484	246	238	22.12	26.55
Jews . . .	115	54	61	22.42	28.23
Total . . .	599	300	299		

In Table VII, the figures for the last decade, namely from 1915 to 1924 inclusive, show clearly that the increase in the average percentage of overweight among females in comparison with males is maintained. There is a disproportionate rise in the number of female diabetics, and, in the case of the Jews, they outnumber the males.

TABLE VIII.—1915 TO 1919.

	Cases of adiposity.	Male.	Female.	Average per cent of overweights.	
				Male.	Female.
Gentiles . . .	228	140	88	23.46	27.32
Jews . . .	47	23	24	23.09	31.25
Total . . .	275	163	112		

The figures in Tables VIII and IX indicate that during the decade last passed and more particularly during the latter half of that period (see Table IX), a striking increase in obese females as compared with males occurred. This fact proves that adiposity is a dominant predisposing factor. Our statistics for Philadelphia (presented in Table III) indicate a similar sudden, marked rise in the death-rate among females in recent years. True it is that the mortality from diabetes mellitus among males has also been rising, but not by any means to the same extent as among females. It is of much interest to note that in Table IX, unlike previous ones, the females show a preponderance of adiposity in the grand total and also for both Gentiles and Jews.

TABLE IX.—1920 TO 1924.

	Cases of adiposity.	Male.	Female.	Average per cent of overweights.	
				Male.	Female.
Gentiles . . .	257	104	153	20.03	26.14
Jews . . .	66	28	38	22.35	26.79
Total . . .	323	132	191		

That the significant, decisive rise in the diabetes death-rate and incidence among women is not wholly attributable to the greater adiposity of that sex can be, we believe, proven. For example, when the figures of Table VIII are compared with those of Table IX, it will be seen that the average percentage of overweight among women for the five-year period, 1915 to 1919 inclusive, is greater than that of the next period of the same duration, or 1920 to 1924 inclusive. It is obvious, therefore, that obesity is not the sole causative influence in bringing about the far heavier incidence among women during the last five years. Neither do we believe that the more sedentary lives of females than males alone accounts for the far greater percentage of cases of diabetes among the former sex during that time. While adiposity does not per se explain the marked rise in the prevalence of diabetes in the female during the last five or six years, it is unquestionably the most potent, single predisposing factor in this disease. The greater frequency of diabetes in persons over forty years of age is shown by Tables X and XI.

TABLE X.

	1905-1914				1915-1924.			
	Total number of diabetics.		Number of diabetics over forty years of age.		Total number of diabetics.		Number of diabetics over forty years of age.	
	Male.	Female.	Male.	Female.	Male.	Female.	Male.	Female.
Gentiles . . .	24	18	20	14	27	40	23	31
Jews	10	3	5	2	8	12	6	10

TABLE XI.—DIABETICS—AGE GROUPS BY DECADES.

Age	Gentiles.		Jews.	
	Male.	Female.	Male.	Female.
1 to 9
10 to 19	2
20 to 29	2	..	2
30 to 39	7	9	8	1
40 to 49	16	13	3	5
50 to 59	20	20	5	5
60 to 69	12	9	2	2
70 to 79	2	—	—	—
Total	57	55	18	15

In emphasizing the importance of special preventive measures in the future, Joslin states that wherever sanitary science is at its best, the morbidity of diabetes will be at its highest, because "the disease is fifteen times as common among those over forty years of age as among those under forty years, and the percentage of Americans today over forty is rapidly increasing." While these facts help us to explain the increasing incidence of diabetes in general, they do not explain the much greater rise in frequency of occurrence among females in recent years, since their expectation of life shows no

striking figures over those of males. It is well known that the chief cause of adiposity is the ingestion of foods containing a large percentage of carbohydrates, as sweets, soft drinks, candies and the like.

According to our studies, lack of physical effort is a strong predisposing influence. Heredity also plays a role in from 20 to 25 per cent of the cases. It is conceivable that the nerve strain occasioned by the recent World War fell more heavily on the female than the male sex. It should be recollected, however, that the rise in incidence, as shown by the figures for Philadelphia (Table III) as well as those based on cases personally observed, had been greater among women than men during the war and prewar years, although less pronounced than since that struggle ended. While the strain of the war may have been a potent predisposing factor; it does not seem to us to fully explain the unusually and rapidly increasing prevalence of this disease among women in recent years.

Again, according to our statistical investigations none of the hitherto known predisposing influences either singly or in combination, explains the phenomenal increase in incidence of diabetes mellitus among females during the last five or six years; and it is obvious that the determination of its cause would have an important bearing on the prophylactic treatment of the disease.

Emerson ascribes the increasing diabetes incidence in this country to a lessened per capita use of meat and an increased per capita consumption of sugar, cereals, milk, vegetables and fruits. He also supports the contention of Allen by statistical evidence, that much diabetes is due to a fatigue of the function of carbohydrate tolerance by an attempt to assimilate a diet which overstrains this function.

That the greater prevalence of diabetes has been encouraged by changes in food habits is an assumption further supported by a considerable amount of evidence. For example, Taylor⁷ points out that not only an increased per capita sugar consumption, but also that of fruits has taken place coincident with a reduction of the per capita use of meats. Riesman⁸ holds that the cause of the increase of diabetes is the greater per capita sugar consumption coupled with the increase of sedentary habits among most classes of people. The habitual ingestion of too much food causing a gain of weight is a potent factor. The foregoing views, however, fail to take account of the fact that such dietetic changes have most probably affected males as well as females, although possibly to a less extent.

It is well known that certain diseases other than diabetes have similar characteristics, for instance, exophthalmic goiter, which has shown an increased frequency of occurrence during recent years (although less marked than diabetes), and a higher incidence among females than males. In both we are concerned with disorders of endocrine function.

It is known that extirpation of the pancreas is invariably followed by all of the clinical indications of diabetes mellitus and also hyperglycemia. That the influence of the pancreas in carbohydrate metabolism is due to an internal secretion, the product of the islands of Langerhans, is a statement which will command universal agreement. The increased tolerance for carbohydrates often acquired by diabetics as the result of fasting, leaves little room for doubting that the disease of the pancreas giving rise to diabetes is often a functional one during its earlier stages at least. It is equally clear that while the pancreas supplies something which normally enables the tissues to utilize sugar, there would seem to be a number of agencies capable of interfering with this function. The significance of these factors, which induce fatigue of the function of carbohydrate tolerance, however, is not definitely known.

Summary. From these statistical studies, it would appear that the death-rate of diabetes in Philadelphia had been increasing steadily until checked by the use of insulin about the middle of 1923, and that its incidence in patients under our personal observation, has been increasing steadily up to the end of 1924 among females. Whereas in 1913, the numerical rating of diabetes as a cause of death assigned it to twenty-second place, ten years later or in 1923, it occupied twelfth place, corresponding with what was found in the Registration Area of the United States and in New York in 1920. According to our findings after the age of forty, women showed a decidedly higher diabetic death-rate and heavier incidence than men during the past two decades, while for the like preceding period, the preponderance of deaths from this complaint occurred among males. This change in the influence of the sexes upon mortality-rate of diabetes is one of the most interesting facts in medicine and, moreover, no satisfactory explanation can be offered for it. In our series of 1306 cases of adiposity, which includes 119 cases of diabetes, this sex relationship was also noted with respect to the incidence of the disease. The excess of deaths among females has progressively increased in Philadelphia in recent years until the sex ratio reached approximately 2 to 1 in favor of females.

The predominant effect of adiposity as a predisposing cause of diabetes is clearly indicated by the accompanying tables, although it is to be recollected that only 1 in 12 obese subjects develop diabetes among Gentiles, and 1 out of every 8 among Jews. Whether the higher ratio among the Jewish race is owing to greater susceptibility to the disease or a relatively greater degree of overweight alone, as Joslin believes, is perhaps still an unsettled question. We believe that the phenomenal rise in the diabetes death-rate and incidence among women in recent years, as shown by the statistical studies of Emerson and Larimore and also our own figures, is not due solely to their greater and more general adiposity. For example, it is shown by our statistics that the cases of diabetes have multiplied

themselves five times since 1880; but it cannot be justly claimed that overweight has increased in degree to a like extent. Again, on comparing Table VIII with Table IX this statement is strongly corroborated. Finally, in 18 per cent of our cases of diabetes, the disease occurred in persons of normal or even subnormal weight.

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**PROBLEMS IN THE DIAGNOSIS AND TREATMENT OF INFILTRATING TUMORS OF THE CEREBRAL HEMISPHERES,
WITH REMARKS ON A NEW SURGICAL
PROCEDURE.***

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IN spite of the advances in the surgery of the brain—advances which may be called remarkable and in which the part played by American neurosurgeons may be pointed to with justifiable pride—little progress has been made in the surgical treatment of infiltrating tumors of the cerebral hemispheres. In a large number of the patients, the exposure of the brain and the tumor, after a large osteoplastic bone flap has been turned down, reveals a condition of affairs which is beyond remedy by surgical means.

In those forms of infiltrating tumor in which, for reasons not yet well understood, the neoplasm has undergone degenerative changes with the formation of a small or large cystic cavity lined by a thin or thick wall of gliomatous tissue, the outlook for therapy is a little better. Some of these cystic gliomas can be incised, their contents evacuated, knobs or masses of tumor tissue excised, the walls of the cyst cauterized with Zenker's solution or some other

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fixative, and the patients benefited and sometimes relieved for many years.

Occasionally, as in the case illustrated in Figs. 1 and 2, a pedunculated tumor lies within a cyst cavity, and the mass together with the thin wall of the cyst can be radically extirpated.

In still other patients, the cyst cavity can be emptied after it has been punctured with a needle, and the contents can be evacuated at regular intervals by a simple puncture of the cystic cavity. (Figs. 3 and 4.)

Some of these cystic gliomas run a slow course after the fluid contents have been removed: the patient is relieved of most or even of all of his symptoms for one to two years or longer.

The results of attempts at radical excision of solid infiltrating growths have mostly been disastrous failures. In rare instances, the growth is small and in a location where excision is possible; but in most of the patients, the growth is so large that it cannot be completely excised and even if a radical excision be possible, extensive loss of function is certain to follow.

A few years ago, I carefully studied all of the brains with infiltrating tumors in our collection, and found only a single specimen in which the growth was small enough or so situated that its complete removal would have been possible. The results of extensive excision of entire lobes of the cerebrum have not been satisfactory even in the hands of the most enthusiastic advocate of such radical resection of the brain, and the operation is rarely a justifiable one.

Occasionally, in a deeply subcortical infiltrating neoplasm which has grown toward the surface of the brain, the superficial portion of the growth is not infiltrating but has well-defined margins. In these patients the superficial part of the growth can be peeled out of the cortex in the same way as is done with an endothelioma, but when the deeper part of the growth is reached, it is found to infiltrate the subcortical tissues, so that only the superficial part of the growth can be removed. After the excision of the superficial part of the tumor, there may be, for a time, considerable improvement, but in most instances the improvement is not as much due to the partial excision of the growth as to the decompressive effect of the entire surgical procedure.

The largest number of fatalities after operations for brain tumor occurs in patients with surgically irremediable subcortical infiltrating growths, although the dangers of exploratory operations have been definitely diminished by the use of local instead of general anesthesia.

If it were possible to exclude from the category of cases which require major operative interference many of the hopeless infiltrating growths, the results of brain tumor surgery would be much improved.

Consider how much would be gained if such a selection of cases would be possible. How many patients and their families would be saved from the stress and strain of the surgical procedure? How

great would be the economy of time and energy? It is a great waste of energy for the surgeon to perform an operation which often requires several hours, only to find a surgically irremediable condition. Likewise, the time of assistants and of nurses and the amount of surgical materials used for such an operation are economically far in excess of what is accomplished by the surgical procedure.

If it were possible to make the diagnosis of an infiltrating tumor very early when the growth is still a very small one, and further, if one could determine before hand that the small infiltrating neoplasm was entirely in or near the cortex, something could perhaps be done by surgery. Such a consummation, devoutly to be wished for, is as yet impossible. I am therefore convinced that the next advance will come from the better recognition of, and discrimination between, meningeal growths on the one hand and subcortical infiltrating growths on the other.

The entire problem resolves itself into the question: How often will it be possible to make the diagnosis "subcortical infiltrating tumor" before the operation with sufficient certainty that a major exploratory operation can be avoided?

In attempting to answer this question, it is logical to speak first of the neurological symptoms and signs of subcortical growths, and the possibility of a diagnosis being so certain that exploratory operation can be refused. In some patients, the diagnosis can be made with certainty, in others it can be suspected, but in very many cases the patient is given the benefit of the doubt, and a major exploratory craniotomy is advised. No doubt the time will come when the signs and symptoms of subcortical infiltrating growths will be much better understood and the clinical picture of this type of growth more clearly defined, so that a positive diagnosis will be made more often than is possible today.

The purpose of this paper is not to discuss the purely neurological aspects of the problem, but to consider the part that the neurosurgeon should take to lessen the number of exploratory operations.

1. The Study of the Roentgenograms of Patients in Whom Air has been Injected into the Ventricular Cavities. The injection of air into the ventricles and ventriculography, in spite of the dangers, is of value not only for the localization of otherwise unlocalizable growths, but also for the differentiation of subcortical from superficial neoplastic disease.

For the past year, Dr. Silbert and I have been making casts of the lateral and third ventricles of the brains of patients who have died from tumors, have studied the finer changes in the shape and size of the lateral ventricles, and have compared the actual casts of the ventricles with the ventriculograms of the patients taken before death. We then correlated the data obtained with the size, shape and location of the tumor, and finally attempted to explain



FIG. 1.—L. L., Neurological Institute. A pedunculated tumor within the cavity of a gliomatous cyst shown by pneumography—lateral view.



FIG. 2.—L. L., Neurological Institute. A pedunculated tumor within the cavity of a gliomatous cyst shown by pneumography—antero-posterior view.



FIG 3.—P. H., Neurological Institute. An irregular shaped cavity of a gliomatous cyst shown by pneumography—lateral view.



FIG. 4.—P. H., Neurological Institute. An irregular shaped cavity of a gliomatous cyst shown by pneumography—antero-posterior view.

the objective neurological disturbances including the papilledema in each eye by the comparison of the changes in the ventricles, the size and location of the growth and the changes in the size of the two cerebral hemispheres.

These investigations have taught us a number of valuable facts regarding the mechanical effects of supratentorial growths and have led us to more fully appreciate the changes seen in the ventriculogram. Our studies are far from concluded, but a preliminary report will be published in the near future.

As is well known, superficial growths—especially the endotheliomata—may deform one or both lateral ventricles. A meningeal growth over one frontal lobe may collapse part of one or both anterior horns; one over an occipital lobe or on the under surface of a temporal lobe may collapse the posterior or inferior horn of the homolateral lateral ventricle, but it is more rare for such a meningeal growth to cause much distention of the opposite lateral ventricle or of that of the same side.

If an endothelioma is so placed as to make pressure upon one or both foramina of Monro sufficient to occlude one or both of them, distention of one or both lateral ventricles may follow and even part of or the entire contralateral ventricle may be shown to be dilated. This is, however, relatively very infrequent. Subcortical growths, on the other hand, both on account of the tumor and of the hyperplasia of the lobe, usually cause a well-marked dilatation and often a dislocation of some part of the contralateral ventricle. Therefore, in a suspected hemisphere growth, a marked dilatation of the contralateral ventricle makes it more probable that the growth is subcortical and therefore infiltrating.

Furthermore, there is, as should be the case, a definite relation between the location of the tumor, the amount of distention of the anterior, posterior and inferior horns of the contralateral ventricle, the degree of fundus changes in each eye and the disturbances in function on both sides of the body. The details of all of these changes will be given in full when Dr. Silbert and I publish the results of our studies, but I have made mention of this fact only in order to remind you that the value of ventriculography is not only to localize an otherwise unlocalizable growth, but also to distinguish between meningiomas and subcortical tumors. When the time will come, as it surely will, that we shall be able to obtain stereoscopic roentgenograms of the ventricular system after the injection into the ventricles of a nonirritating fluid which is impermeable to the roentgen-ray, instead of air, the information we shall be able to obtain from ventriculograms will be much greater than it is today. We have been investigating this problem for many years, and, no doubt, others are making a search for a fluid that can be injected into the ventricular cavities for this purpose.

2. **Calcification**, visible on the roentgen-ray films occurs in a small number of subcortical infiltrating growths, and the appearance of this calcification is very characteristic and should be recognized. Dr. C. W. Schwartz, the director of the Roentgenological Laboratory of the New York Neurological Institute, and I have been carefully studying the changes visible in the roentgenograms of the skulls of these patients. The shadows are usually very slight and can often only be recognized on stereoscopic examination. The calcification is usually rather diffuse without distinct borders, and irregular in shape and outline. Its appearance is different from that of calcified cysts of the pituitary body, or of the calcification seen in so many craniopharyngeal pouch tumors. It has a different appearance from the calcification of the falx cerebri or other parts of the meninges, so often seen on roentgen-ray films, and the stereoscopic examination of the films shows that the shadow seen is within the substance of the one or the other hemisphere.

3. **The Surgical Procedures Recommended in Suspected Subcortical Hemisphere Tumors.** The main object of this paper is to recommend as a regular surgical procedure, one that differs from that ordinarily performed by the neurosurgeon.

In most of our operations for supratentorial infiltrating growths, we have been accustomed to turn down a large osteoplastic flap in order to expose and explore the part of the brain in which the tumor is presumably located. The growth is found either infiltrating the cortex, or is demonstrated to be subcortical by puncture or by actual incision of the exposed brain, or the puncture of the brain fails to demonstrate any pathology. In the majority of these patients the operation is concluded with the aspiration of a cyst cavity, the injection of air into a cyst cavity in order to determine the size and extent of the cyst by roentgen-ray, or if the growth is not cystic, by the removal of a specimen, by the making of a subtemporal decompressive opening, or by the removal of part of the bone flap overlying the growth for the purpose of later roentgen-ray or radium therapy.

Instead of this major operative procedure, and it is a major surgical interference, even if done under local anesthesia, I suggest that the following method be adopted as the regular procedure: Under local anesthesia, an incision is made through the scalp in a location and direction that it may form part of the line of incision for the outlining of an osteoplastic flap, if that be later required. Through this primary short incision, a button of bone is removed with the trephine and a small incision, sufficient to permit the passage of a blunt brain puncture needle, is made in the dura.

If no tumor is found directly under the opening in the dura, the subdural space is carefully explored in various directions with a broad flat probe made of German silver and bent so that it can be passed underneath the dura. For this purpose, the blunt cannula

devised for puncture of the corpus callosum can be used. The majority of endotheliomas are adherent to the dura, have buried themselves, more or less, in the brain, and lie over the convexity of the hemispheres near one of the large venous sinuses. More rarely, the growth develops from the dura over the cribriform plate of the ethmoid, from the falx between the two hemispheres, or from the dura underneath a frontal, temporal or occipital lobe.

If a distinct, firm resistance is felt by this subdural exploration—as would occur in the presence of a meningeal tumor—then the surgeon at once proceeds to anesthetize a large area with novocain solution, to divide the scalp and to make a large osteoplastic bone flap. If no resistance is met with, the brain itself is punctured in several directions with a blunt ventricular puncture needle.

If the puncture is slowly and carefully done, slight differences in the resistance to the passage of the needle can often be appreciated and the location of the tumor determined by this means. The resistance is usually a very slight one unless intracranial tension is very high and only slight pressure is needed to advance the blunt-pointed needle after the piaarachnoid has been penetrated. If the passage of the needle is arrested by a firm resistance, there is never any doubt that a tumor or the wall of a cyst or perhaps the wall of an abscess cavity has been reached.

If a cavity which contains the typical yellow fluid which occurs in a gliomatous cyst is entered, the fluid is emptied by aspiration, and air is injected in order to obtain a roentgen picture of the cyst cavity, and the small incision in the scalp is then closed by suture and the patient sent to the roentgen-ray room.

If, on the other hand, no resistance to the passage of the blunt needle is encountered (and this is often the case), the small plugs of brain tissue obtained by aspiration are carefully preserved in formalin for histological examination, the direction in which the needle was passed and the depth to which it was inserted carefully noted, and the operation concluded for the time being.

If air has been injected into the cavity of a gliomatous cyst, stereoscopic lateral and one antero-posterior roentgen-ray films are taken.

The further course of the procedure will depend upon the results of the roentgen-ray and the laboratory examinations. After a few days, if the roentgen-ray shows that the cyst is near the cortex and does not extend deeply into the brain, an osteoplastic flap is made under local anesthesia, the size of the flap being only sufficient to expose part or all of the cyst whose exact location and size have been determined by the roentgen-ray. At this second operation, the cortex is incised down to and into the cyst, the lining wall partly or entirely excised if that be possible, or the inner wall cauterized with a fixative such as Zenker's solution.

Should the roentgen-ray show that the cyst is deeply subcortical

and especially if it extends deeply into the centrum ovale and perhaps across the midline, no second operation is attempted. The puncture of the cyst and the emptying of its contents at regular intervals will give the best results. If the cyst is of considerable size, sufficient relief of pressure is obtained by the evacuation of the cyst fluid, and only in rare instances is there need for an added subtemporal decompression.

Finally, if there is no evidence at the primary brain puncture of a cyst and if the histological examination of the tissue obtained by aspiration revealed that the growth was a glioma or its more malignant form, spongioblastoma, further operative procedures are generally useless. In the attempt to relieve headache, to save failing vision, or to prevent a rapidly progressing paralysis, we have often, primarily or secondarily, done a subtemporal decompression.

During the past two years, we have followed this plan of procedure in a number of patients with suspected subcortical brain tumors. Sometimes, as in a recent case, I have found that we were dealing with an endothelioma and then the radical operation was at once proceeded with. In another patient, operated upon a few weeks ago, we felt a resistance with the puncture needle and at once proceeded to make an osteoplastic flap, only to find that the growth was an infiltrating one in the cortex. In a number of patients, either a gliomatous cyst was demonstrated by the puncture through the trephine opening, which was near the cortex so that it was dealt with at a second operation, or it was so deeply placed and so extensive that a radical procedure was out of the question, or finally the aspiration of the brain withdrew tumor tissue from the depth and the minor operative procedure clearly showed that no satisfactory result could be expected from a major osteoplastic craniotomy.

In another paper, I shall describe the surgical procedures more in detail and shall report in full on the number of patients who have been saved from a major cranial operation; the number of instances in which the minor operation has given us all the information that could have been obtained from a major osteoplastic procedure, is rapidly increasing.

Multiple exploratory brain punctures through small openings were, many years ago, recommended for the purpose of finding an otherwise not localizable growth, but the object of the puncture here advised is to determine rather the nature and the relations of a growth which has already been localized by other means.

I am fully cognizant of the fact that, theoretically at least, a very small removable growth might not be found by the procedure here suggested—a procedure which is exactly like that now used for exploration for suspected brain abscess. The only instance in which an exploration may reveal a small tumor is one in which an endothelioma develops over part of a motor area with convulsive

attacks of the Jacksonian type, and in such a patient the indications for a primary osteoplastic craniotomy are undoubted. These cases are, in the present state of our knowledge, unusual; in most instances, the endotheliomas found and removed at operation are of considerable size.

In those patients in whom the course of the symptoms is characteristic of a cortical growth, in whom there are changes in the overlying bone (erosion of the inner table, cranial hyperostoses, localized enlargement of the diploic veins, and so forth), the diagnosis of cortical growth is so well founded that no preliminary puncture exploration such as I have described is necessary. Likewise the procedure should not be applied to growths of the pituitary, to tumors on the floor of the third ventricle or within the ventricular cavities.

If all of these cases—the probable endotheliomas, pituitary tumors, craniopharyngeal pouch and intraventricular tumors—be excluded, there remain a group of tumors of which at least 90 per cent are subcortical and infiltrating. If one considers, further, that as already mentioned, the majority of the meningeal growths are of considerable size, the conclusion is justified that the chances of missing a removable tumor by the exploration through a small opening which is here recommended, are very small. If such a meningeal growth lay between the two hemispheres or on the under surface of a frontal, temporal or occipital lobe, it would almost certainly be felt as a firm resistance when the affected lobe of the brain was punctured with the blunt needle even if no obstruction was met with by the subdural exploration.

One might argue that exploratory puncture, after a bone flap has been turned down, will allow the surgeon to puncture the brain at both the anterior and the posterior borders of the exposed dura, and therefore the chances of finding the growth should be better than through a single trephine opening.

Theoretically such an argument is well founded, but practically, if the localization of the growth has been even approximately correct, the tumor should be reached by the puncture exploration through a small opening, and this view is supported by my experience in a not inconsiderable number of cases. If the localization of the new growth was entirely incorrect, if a presumed frontal neoplasm were in reality in the posterior cranial fossa or if a growth were in the opposite hemisphere to that in which it had been localized, it would be missed as well by the puncture exploration as by the actual exposure of part of the brain by an osteoplastic procedure. Such gross diagnostic errors are, however, of rare occurrence.

If the puncture disclosed that there was a well-marked dilatation of the lateral ventricle, it would at once lead the operator to suspect that the tumor was either in the opposite side of the brain or was deeply located so as to exert its pressure upon one or both foramina

of Monro or upon the ventricular pathway caudad to this region, and the operation should then be, for the time being, concluded with the injection of air for ventriculography.

Finally, a few words should be said on the subject of the dangers of puncture of the brain in subcortical infiltrating tumors. In spite of the apparent innocuousness of puncture of the brain with the object of emptying of dilated ventricles in the course of operations for supratentorial or infratentorial disease or for the purpose of the injection of air, the number of times in which a needle is passed into the brain substance should be kept as small as possible. Undoubtedly a bloodvessel may be injured and bleeding into the brain may occasionally follow, and the possibility of hemorrhage into a tumor after the puncture of the growth must always be kept in mind. Whether or not the brain has been exposed by an osteoplastic flap, the surgeon must perform the puncture in the search for a subcortical neoplasm and the danger from a puncture through a small opening is no greater than that done after a large osteoplastic flap has been turned down.

Conclusion. The procedure that I have described is recommended with the hope and belief that it will materially diminish the number of useless major exploratory operations for supratentorial new growths, and that by this means the indications for operative interference will not only become more clearly defined but also that the results of the surgery of tumors of the brain will be improved by the exclusion of surgically hopeless intracranial disease.

LEPTOSPIROSIS ICTEROHEMORRHAGICA (WEIL'S DISEASE).

By JOSEPH SAILER, M.D.,

PHILADELPHIA.

With a Bacteriological Note by J. C. SMALL.

(From the Medical Wards and Bacteriological Laboratory of the Philadelphia General Hospital.)

ON August 15, 1922, I was asked by Dr. Wm. M. Lashman, of Camden, N. J., to see with him a man aged fifty-one years. He had been sick nine days with chills, fever and pains all over the body. Jaundice has appeared early and had become steadily deeper. The pains became more severe and he felt and gave the impression of being gravely ill. The physical examination yielded little, but was nevertheless important. The jaundice was intense, involving the skin, sclera and mucous membranes. The throat, head and lungs were normal. The liver was not perceptibly enlarged nor

was anything important found in the abdomen. The reflexes were normal. There was some diffuse tenderness all over the body and the calf muscles, in particular, were exquisitely tender, so much so that he objected to a second attempt to squeeze them.

I suggested the possibility of Weil's disease and the following day Dr. Rubinstone examined the patient's blood by dark-field illumination and found a few typical parasites, although it was then the tenth day of the disease. It was my intention to have the urine also examined, but unfortunately the specimen taken to Dr. Rubinstone's office was spoiled during transmission and it could not be used. Laboratory examinations were difficult. The Wassermann test was negative, the urine contained a slight amount of albumin and bile, and the differential count of the white blood cells showed 70 per cent of the polymorphonuclear forms. Dr. Lashman informed me that the patient made an uneventful recovery.

On October 3, 1924, a white man, aged forty-four years, was admitted to my wards in the Philadelphia General Hospital. One week previously he had been drenched in the rain. He had sudden headache, went to bed and felt stiff all over. The next day he vomited and his nose began to bleed, and this continued for two days. The pain in the muscles of the lower limbs was severe, and extended from the hips to the ankles. He was told by his neighbors that he was turning yellow.

The previous history included measles, mumps and pertussis during childhood, a chancre at seventeen, a left inguinal bubo, requiring an operation at eighteen, and several attacks of gonorrhea. At the age of thirty-six he had begun the use of morphin, and had twice been in institutions for the cure of this habit, both times unavailingly. He had always used alcohol to excess, when possible to obtain it. In 1923 he was cut under the eye in an automobile accident. He lived in the cheapest lodging houses.

The findings of the physical examination were: Cyanosis of the lips, ears and fingers, yellow and injected skin and sclera, normal throat, heart and lungs, a liver that could be palpated 3 cm. below the costal margin. The urine contained a trace of albumin, hyalin and granular casts, a few red blood cells and bile pigment. There was slight anemia, no leukocytosis, normal blood chemistry. Hemolysis of erythrocytes began at 0.46 per cent and was complete at 0.26 per cent sodium chlorid solution. The van den Bergh test was positive for obstructive jaundice. An attempt to obtain the duodenal contents was unsuccessful.

On October 4, about the eighth day of the disease, and the second day of his stay in the hospital, some urine, obtained as aseptically as possible without catheterization, was injected into a guinea pig, and fifteen days later a report was received from the laboratory that the leptospira icterohæmorrhagica had been isolated from the urine of the guinea pig and the diagnosis of Weil's disease confirmed.

The subsequent course was one of rapid improvement, and on October 10 he was discharged at his own request.

Discussion. In 1886 Weil reported 4 cases of a peculiar disease, 2 of which had been observed in 1870 and 2 in 1882. The patients were all men, 3 of whom were twenty-two years and 1 twenty-three years of age. The symptoms in all cases were similar and consisted of fever, prostration, headache, dizziness, anorexia, severe pains throughout the body, especially the limbs, vomiting after the administration of calomel, diarrhea and jaundice. The spleen and liver became enlarged during the course of the disease; the urine contained albumin and casts. The fever lasted for six, nine, nine and twelve days, and in 3 of the cases a mild relapse or recurrence was observed. All the patients recovered. He discussed various diagnoses, particularly acute yellow atrophy of the liver, relapsing fever, yellow fever, bilious typhoid, a condition that had been described by Griessinger, and renal typhoid. Although he admitted that it had close affinities to abortive typhoid with jaundice and nephritis, he concluded that it was probably a *morbus sui generis*, but he did not suggest any name for it.

Subsequently many cases were reported which added three facts to Weil's description; that the disease was epidemic, that many of the patients were butchers, and that the muscles were tender, especially the calf muscles.

A febrile disease, with jaundice and often occurring in epidemics was not new. Indeed it had been described in the eighteenth century, and as early as 1812 in the United States, and many times in European medical journals. (Noguchi,^{18, 19} Blumer,² Heiser,⁷ Valassopuolo²⁰). Weil, however, focussed attention upon it and described more accurately its symptoms and course.

In 1914 five Japanese investigators (Inada *et al.*¹¹) stated that earlier in the year they had discovered in the blood and urine of patients suffering from the disease Odan-eke, a name that means icteric pestilence, a spirochetal organism. To this organism they gave the name *Spirochæta icterohæmorrhagica* and proposed the name spirochetosis icterohemorrhagica for the disease. This spirochæta is intensely pathogenic for guinea pigs and has been transmitted from one to another with persisting virulence 51 times. In the tissues of the guinea pigs it is found most abundantly in the liver, and an emulsion of the liver, if injected into susceptible animals, produces a fatal disease characterized by jaundice. The organism is pleomorphous: it is only visible by the dark-field illumination, and it stains by the Levaditi and other methods employed for spirochæta: it passes through the Berkefeld filter and grows on the Noguchi media. It penetrates the intestinal mucosa, and what is more remarkable, can penetrate the shaven abdominal skin of a guinea pig in five minutes or less. I suspect that it is possible for it to penetrate also human skin. It is found in the blood of the

human patient until the seventh day, and subsequently escapes by the urine, in which it can be found until the fortieth day, and exceptionally even longer. The blood of the convalescent patients possesses bactericidal properties, and numerous experiments were performed to discover an immune serum. The immune bodies appear from the fourteenth to the twenty-eighth day of the disease and persist at least as long as five and a half years. An immunized goat produced a serum with curative and protective properties. Arsphenamin was of doubtful use.

Another group of Japanese investigators (Ido *et al.*^{9, 10}) were able to produce active immunity in guinea pigs, which is the most susceptible animal hitherto discovered, and none of which normally survive inoculation. They used livers from inoculated guinea pigs emulsified in 0.5 per cent carbolic acid and kept in an ice box for a week. This so attenuated the virus that it was possible to inoculate guinea pigs with it, and these would survive, and could subsequently be inoculated with fresh liver containing active *Spirochæta icterohæmorrhagicæ* without fatal results. Horse serum, obtained from horses inoculated with the organism, protected guinea pigs, and, injected into men, caused immune bodies to appear in their blood, but guinea pigs into which it had been injected did not develop immune bodies until they had received and had survived injections of living *Spirochæta icterohæmorrhagicæ*, a fact which may bear some relation to the greater susceptibility of the guinea pig. This horse serum was also apparently useful in curing cases of Weil's disease among human beings.

Still another series of studies by the Japanese (Inada *et al.*^{12, 13}) determined that serum from immune goats inhibited the disease in all cases if injected before the appearance of jaundice. Thirty-five cases of Weil's disease were treated with serum. Seven deaths occurred, but 1 of these was moribund when admitted, and 2 died of accidental complications, so that the actual mortality was 12.5 per cent; the usual mortality in Japan being 30.6 per cent. It was found that the serum decreased the infectivity of blood drawn on the fourth day of the disease, and absolutely destroyed all the *Spirochæta icterohæmorrhagicæ* in the circulation. It was necessary to inject fairly large doses, 60 cc in twenty-four hours. The course of the disease is said not to have been affected, which I assume means that the duration of the fever was not shortened. They found that arsphenamin was useless (Futaki *et al.*).

In 1915, one year after its discovery in Japan, but before this discovery was known in Europe, Hübener and Reiter⁸ discovered an organism with cilia in the blood of a patient suffering from Weil's disease. It was 5 microns in length and resembled a trypanosome. This organism was pathogenic for guinea pigs, and mildly pathogenic for apes and rabbits. In a later paper they suggested the name *Spirochæta nodosa*. Doubtless had they had more material than

one human case, they would have studied the organism completely; as it was, they merely confirmed the Japanese workers. They claim, however, that in guinea pigs, arsphenamin, although it does not prevent, at least delays, death.

In 1917 Noguchi,¹⁸ having obtained living organisms from Japan, Belgium and the American wild rat, made a careful study of all. He found that it differed from other spirochæta in having more twists, in being actively motile for three months in firm agar media, and in resisting 10 per cent saponin solutions. Therefore it should be considered a new species and he suggested the name *Leptospira icterohæmorrhagica*, and this has been generally adopted. He found also that the leptospiræ from the three sources were probably identical for they conferred cross immunity. Inoculated guinea pigs died in from nine to twelve days and they had jaundice, choluria and extensive visceral hemorrhages. The leptospiræ were found in the organs, rarely in the blood, and in varying numbers in the urine. Apparently nothing of importance has been added since this paper.

Weil's disease, then, is a specific infectious condition caused by the *Leptospira icterohæmorrhagica*. This organism is found in the wild rat in many, and probably in all parts of the world. In Japan it is found in 39.5 per cent of the house and ditch rats, in America, Jobling and Eggstein¹⁵ found it in 10 per cent of the wild rats of Nashville, Tennessee; and Noguchi¹⁹ found it in the rats of Guayaquil and New York. Host and parasite apparently live in perfect amity, for there is no reason to assume, from the reports of the investigators, that the rats are in any way disturbed by the leptospira. The parasites escape by the urine and infect the soil, particularly if it is wet, and the disease may also be communicated by rat-bite, at least two guinea pigs bitten by infected rats developed the disease. The disease is more common in individuals working in places infected by rats, thus in Europe and America it occurs especially among butchers, in Japan among cooks and miners.

The symptomatology, as described by various observers, although essentially the same, nevertheless varies in some particulars. Valassopuolo²⁰ recognizes four stages: (1) Spontaneous pains in the muscles, dysphagia, erythema, and injection of the conjunctivæ. (2) Icterus (this he states, in agreement with Dawson, may be absent), oliguria, and in the urine albumin, casts and blood are found, and rising fever. The erythema stops when the jaundice appears. (3) The urinary crisis occurring about the seventh or ninth day, the amount of urine rising to 2 liters per day and even more exceptionally to 8. During this time the fever diminishes. (4) The stage of convalescence. The fever is usually remittent, there may be hemorrhage from the nose, gums and into the skin.

Dawson *et al.*³ speak of the initial chill, the pain behind the eyes, the high fever, 103° to 105°, and vomiting in the early stage. He mentions the enlarged liver and palpable lymph glands; the rare

enlargement of the spleen. Jaundice occurred usually on the fourth day. Hemorrhages occurred in 14 of 18 cases, herpes labialis in 40 per cent of the cases. There is leukocytosis. The pulse is slow. Rare complications are retention of the urine in 3 cases and auricular fibrillation in 1 case.

Gwyn⁶ mentions that the onset may be acute or gradual. Chills occurred in only 7 of 13 cases. All cases had prostration, headache, nausea and vomiting, and nearly all had abdominal pains. He lays great stress upon the muscle pains, which he regards as possibly due to myositis, caused by infection of the muscles by the parasites and this should be investigated, for it is an interesting suggestion. The muscles may be swollen as well as tender. He further suggests that myositis without jaundice may be caused by leptospira.

In addition to the jaundice he notes a scarlet flush, herpes labialis, a few rare eruptions, and lays emphasis upon the injection of the conjunctivæ. Delirium, coma and convulsions were noted in a few patients. Hemorrhages were common but purpura rare. The liver and spleen were seldom palpable. The urine contained albumin and casts. There was mild leukocytosis. The pulse rate was usually slow.

These three papers are especially quoted because all are based upon personal contact with the disease.

Basile¹ thinks that the jaundice is hemolytic, Heiser⁷ believes that it is obstructive and caused by a plug of mucus in the common bile duct direct. The van den Bergh test in my second test agreed with this opinion. Jones and Minot¹⁴ also indirectly support this view because they find that in the early stage, the duodenal contents contain very little bile and in the latter stage a large amount. Dawson *et al.*³ state that the leptospira may cause the disease without producing jaundice. The diagnosis should not be difficult. If a patient has fever, jaundice and pain in the muscles, the leptospira should be sought, and if it is not found in the blood, by proper methods it can, if present, be found in the urine.

The treatment is important only in severe cases, and in these the curative serum alone offers any effective remedy. Arsenic and mercury have been suggested, but there is no evidence of their worth.

Prophylaxis is effective. Disinfecting the ground and draining the surface water checked two epidemics in Japan. Any attempt to exterminate rats in this country for the purpose of preventing the occurrence of the disease would be unjustifiable, because it does not constitute any serious menace; but rats carry at least one other spirochæta capable of infecting human beings, *Spirochæta morsus muris*, causing rat-bite fever, and also the bacillus of bubonic plague; and the economic loss that they cause is tremendous. Therefore leptospirosis may be regarded as an additional reason for a nation wide effort to exterminate them. It would be interesting

to know if mice also carry leptospira, but I have found no information upon this point.

The disease is probably not uncommon. Many cases of catarrhal jaundice may be mild forms of Weil's disease and it is possible that myositis without jaundice and with intestinal manifestations and muscular pains also may be due to the leptospira, for Dawson's observations cannot be questioned and are supported by Valassopuolo. When suspected, confirmation should be easily obtained. The easiest method, if a well-equipped laboratory is available, is the examination of the blood by dark-field illumination. This, as my first case showed, may be positive as late as the tenth day, but should be done as early as possible. Guinea pigs are available



Photomicrograph of a section of the kidney of a guinea pig infected by the leptospira icterohemorrhagica, showing stained leptospira just above the center of the picture.

nearly everywhere in America. In the early stage they may be inoculated with the patient's blood, later with the sediment of the centrifuged urine, collected under conditions as aseptic as possible. The leptospirosis of guinea pigs is characteristic. An emulsion of the livers of a guinea pig dying of, or killed during, the disease will infect other guinea pigs and the leptospira can be maintained indefinitely.

Blumer² does not believe leptospirosis is common in the United States though he does not deny that it may occur. In a very careful study of the history of the type of infectious jaundice found here he notes that 72 per cent of the epidemics occur in the fall and winter, that the disease is mild, common in young persons and that the

leptospira is never found. As in his own cases a careful search was made for it by modern methods, this statement is of importance; but it is so at variance with the work in Japan and elsewhere, that, in view of its negative character, it must be accepted, if at all, with great caution. Wadsworth,²¹ however, contributes some supporting evidence. In 300 cases of infectious jaundice studied by his laboratory workers, no leptospiræ were found. The conditions were unfavorable, but one of the laboratory workers, inoculating rabbits with virulent leptospiræ obtained from rats, pricked her finger, had a typical attack of Weil's disease, and *Leptospiræ icterohæmorrhagicæ* were found in the blood. There may be other forms of infectious jaundice but none has been hitherto definitely isolated.

Leptospirosis icterohæmorrhagia has been found in four continents, Europe, Asia, Africa and North America, from Scandinavia (Lapidus and Flaum¹⁶) to the tropics, for the rat is universal and the leptospira seems to accompany it everywhere.

BACTERIOLOGICAL NOTE. *Detailed Report of Study of Urine of Patient P. C.* A sample of about 100 cc of turbid and deeply bile-stained urine was received on October 6, 1924, directly after being voided. The sample was assigned to Mr. Ralph E. Otten, with directions that it be examined for *Leptospira icterohæmorrhagicæ*.

A 50-cc portion was centrifugalized, and the sediment examined by darkfield and by special staining method for spirochetes. Neither of these methods revealed leptospira. The bulk of the sediment was inoculated subcutaneously into a guinea pig. On the eighth day following the injection the animal showed marked jaundice, and appeared weak and inactive. On the morning of the ninth day (October 15) the animal was found dead.

A sample of urine of the guinea pig collected on October 14, showed numerous leptospiræ, demonstrated by staining methods.

Necropsy. Guinea pig, October 15, 1924. The skin, sclera, and mucous membranes of the mouth are deeply bile stained. The subcutaneous tissue, and the deeper tissues and organs show the same deep jaundice throughout. The liver is enlarged and very friable. The spleen is congested and slightly enlarged. The kidneys are congested and grossly show the signs of cloudy swelling. No hemorrhages appear anywhere.

Smears were made from the blood, liver, kidneys and spleen and stained for leptospira with negative results.

Deep tube cultures were made of the blood, liver, kidney, and spleen in 10 per cent horse serum in normal saline; in 10 per cent horse serum in beef infusion broth; in undiluted urine; and in urine diluted with 33 per cent beef infusion broth. In none of these were leptospiræ demonstrated.

Histological sections of the kidney, liver and spleen stained by

the Levaditi method showed small number of the leptospira in the kidney only. (Photomicrograph.)

Comment. The patient (P. C.) presents an interesting case from the standpoint of diagnosis for several reasons: (1) Because of its sporadic occurrence in a city where proven instances of this infection had not been recorded, thereby demonstrating the importance of bearing in mind the possibility of leptospirosis icterohemorrhagica in the study of patients presenting clinical evidences of infectious jaundice; (2) because of the fact that without animal inoculation, the patient's condition would have gone without a confirmed diagnosis. Very careful direct examinations of the urine from this patient failed to reveal the leptospira. This failure of direct demonstration of the leptospira is more to be emphasized in the examination of the blood. The chances for the direct demonstration of the leptospira in a patient's blood, even early in the course of the disease when they are the most plentiful, are not good. On the other hand, it cannot be emphasized too strongly, that confirmation of diagnosis by inoculation of guinea pigs is a very simple procedure, and at the same time a most spectacular demonstration. One might say that the sequence of events in the guinea pig infected with *Leptospiræ icterohæmorrhagicæ* is so definitely pathognomonic that it could scarcely be confused with other conditions, and certainly not so if cultures and microscopic examinations are made of materials secured at the necropsy of the animal.

The third point of interest is illustrated in the results of attempts to demonstrate the leptospira in the tissues of the animal. Even with an undoubted clinical course leading to death of the animal, one is oftentimes disappointed in the failure to demonstrate large numbers of leptospiræ in the tissues. As in this instance, relatively small numbers will be found on prolonged search.

Last, our failure with cultural methods when used upon material containing sufficiently large numbers of the leptospira to afford their demonstration with ease by the direct examination of smears, is of interest. Simpler methods for growing these organisms have been advanced from time to time, and from the descriptions one might be led to believe that such methods would be most useful in confirming the diagnosis in a suspected case. In experienced hands during times of epidemics direct cultures may have a place in diagnosis, but they should never be used in preference to the animal inoculation method, and should certainly never be relied upon for the diagnosis of the sporadic case.

To summarize, the laboratory diagnosis of leptospirosis icterohemorrhagica is simple. It is made by the inoculation of suspected material into guinea pigs, and from the observation of the sequence of events developing thereafter in this animal. The clinical course of the disease in the guinea pig is pathognomonic, but should be confirmed by the more tedious demonstration of the leptospira in the liver, kidney or spleen of the animal.

Blood from the patient should be used during the first four or five days of the jaundice, and injected intraperitoneally in 10 cc amounts into guinea pigs. Afterward, up to the tenth day of the jaundice, both blood and urine should be used for the inoculations. Thereafter one must rely on the presence of the leptospira in the urine only. From 50 to 100 cc of urine should be centrifuged at high speed and the sediment from this injected subcutaneously into guinea pigs.

Summary. Two cases of infectious jaundice are reported in each of which the *Leptospira icterohæmorrhagica* was found. It is believed that they are the first cases occurring spontaneously to be recognized in Philadelphia and its environs.

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A TINTOMETER FOR THE ANALYSIS OF THE COLOR OF THE SKIN.

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A PRESSING need in clinical medicine is a method for measuring and recording the color of the skin. There is perhaps no other type of clinical examination subject to greater error, due in part to the

inability of the physician to describe colors, to the personal equation element in matching colors and to the kaleidoscopic changes in combinations of color exhibited in the skin of human beings.

In reviewing case reports with regard to descriptions of the color of the skin one is struck by the diversity of comparisons. Expressions, such as rose-red, slate-blue, *café au lait*, lemon-yellow, lack clinical accuracy and rank with some of our descriptive terms of size, such as large as a baby's head, an orange or a plum. In attempting clinically to portray the depth of jaundice the need of quantitative and descriptive terms is keenly and constantly felt. There are four main groups of cases in which determinations of skin color are of decided value: (1) In jaundice;¹ (2) in cyanosis;¹ (3) in conditions in which capillary dilatation and increased cell volume play a part, as in polycythemia vera; (4) in various types of pigmentation, as in Addison's disease and hemochromatosis. Furthermore, clinical application of color determination may be helpful in cases of anemia and in cases in which edema is associated.

Determination of the color of the skin is not only important from the standpoint of diagnosis, but it is valuable in following the normal fluctuations of color and those incident to treatment, particularly in the treatment of Addison's disease in which, under the Muirhead regimen, marked variations in the pigmentation of the skin are noted from time to time. This is also true in cases of jaundice, cyanosis and polycythemia.

Possible Approach to the Problem. Two possible lines of approach present themselves in the development of a skin tintometer: A comparison with color plaques, and a spectrophotometric analysis of the color of the skin. The former method consists in reproducing colors of selected areas of skin under controlled conditions by an artist employing water colors. The range of colors is determined separately for each different pathologic group. These are assembled and grouped according to their progressive increase in color. Ten plaques are employed for each scale. Intermediate color plaques may sometimes be determined with a fair degree of accuracy and interpolated by an artist trained in color work. We have been interested in this problem for the last four years, and several such tintometer scales have been developed for use in the study of selected areas of skin and the results recorded in terms of plaques Nos. 1 to 10.

There are several objections to this method: (1) The individual difficulty in matching pigment and skin; (2) the difficulty of recording the values quantitatively; (3) the tendency toward fading and impairment of the color plaques, so that it is difficult to maintain a standard scale. It is evident that the value of such tintometers is limited unless the colors involved are accurately analyzed. Per-

¹ Flagg, P. J.: An Oxyhemoglobinometer for the Clinical Measurement of Cyanosis, Proc. Soc. Exper. Biol. and Med., 1922-1923, 20, 1.

manent value demands that these colors shall be expressed in enduring terms qualitatively and quantitatively. This difficulty is largely overcome by the use of the Munsell system of color analysis.

The second method, that of employing spectrophotometric analysis, may be applicable, but considerable developmental work is necessary to make it clinically adaptable.²

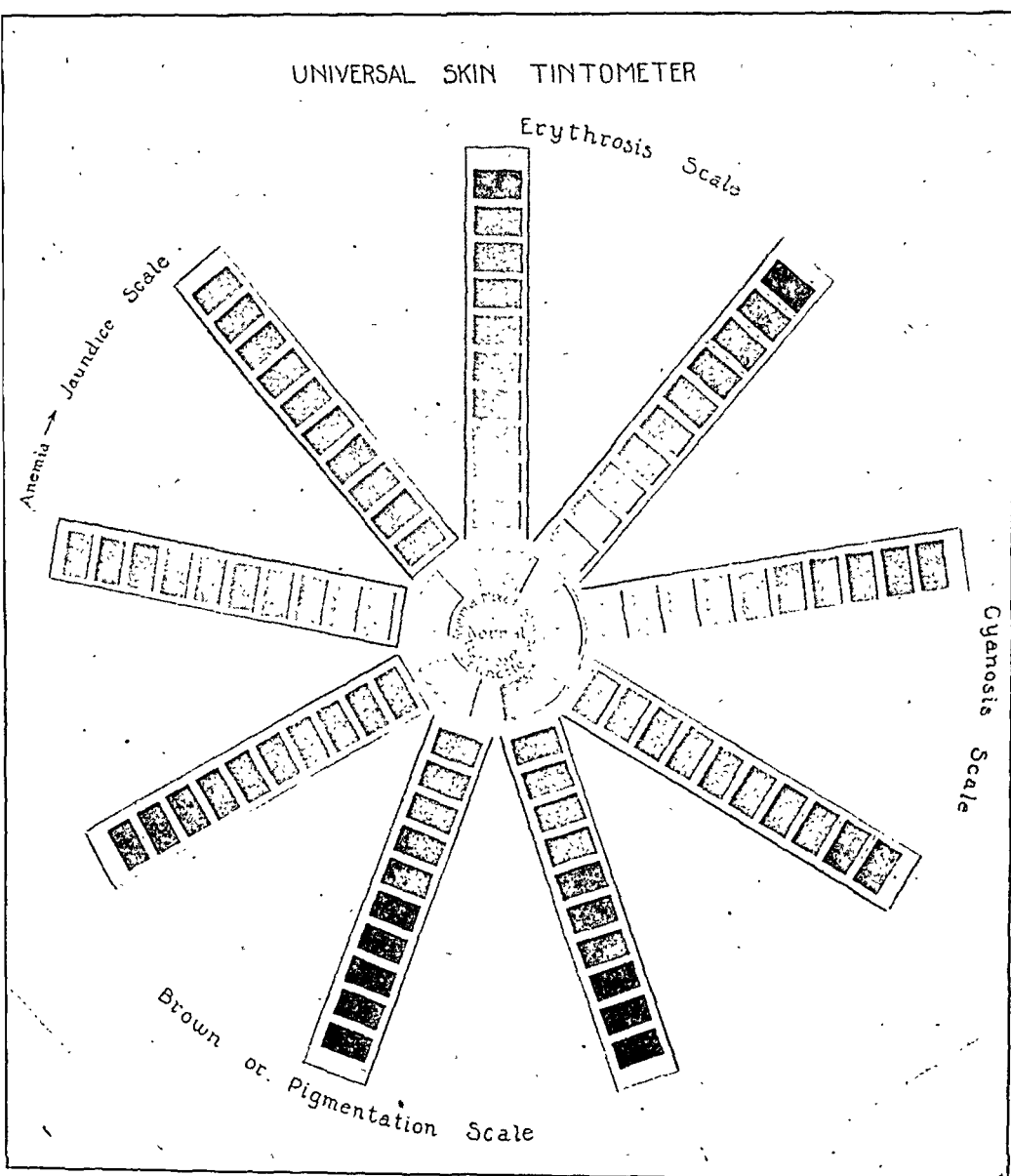


FIG. 1.—Skin tintometer composed of nine separate color scales.

The Method of Developing a Clinical Tintometer. Color reproductions were made under conditions controlled with regard to illu-

² Sheard of the Section on Physics of the Mayo Clinic is attempting at present to develop an instrument of this type.

mination, room temperature, posture, and so forth. The skin areas selected were the back of the hand, over the mastoid process, and the subclavicular zone.

In order to determine normal variations of the skin three groups of normal persons were selected, marked blondes, marked brunettes, and intermediate types. From these, color patches were made which indicated the maximal normal variations. The extremes of

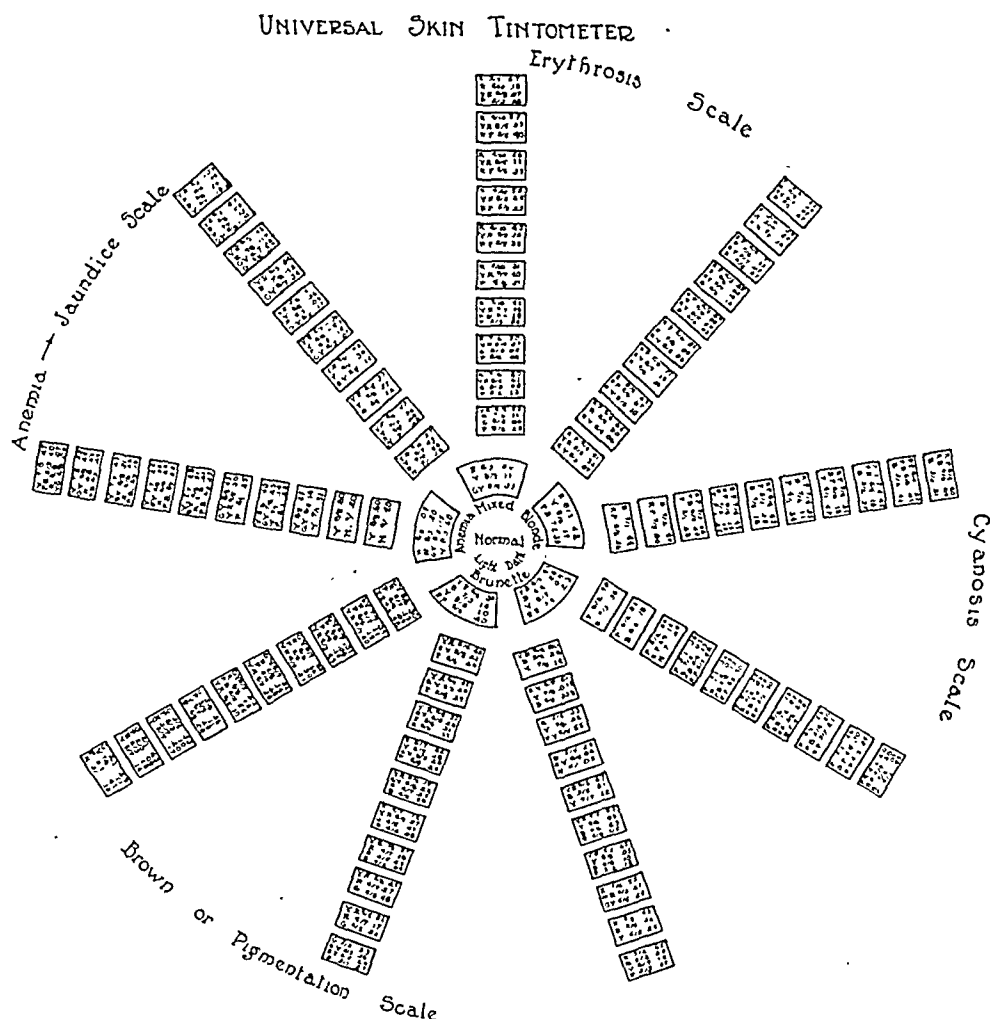


FIG. 2.—Measurements of color plaques comprising the skin tintometer by the Munsell system. Hue is indicated by the aberration of the color, value by the numerator and chroma by the denominator of the fraction.

normal constituted the starting point for the individual color scales. In developing the range of abnormal color and in constructing the tintometer, 10 cases of Addison's disease, 20 cases of polycythemia, 15 cases of jaundice and 10 each of cyanosis, anemia and edema, comprising in all about 100 color studies, were utilized.

Nine individual scales, each composed of ten plaques, were made and assembled in the form of spokes radiating from the central plaques representing the extremes of normal (Fig. 1). It was

found that at least ten colors were desirable for the different color variations observed in certain diseases. Thus there are tintometers for anemia, cyanosis, erythrosis, jaundice and brown pigmentation, each requiring ten to twenty color plaques. In order to determine the accuracy of gradations, and to assign them their correct values,

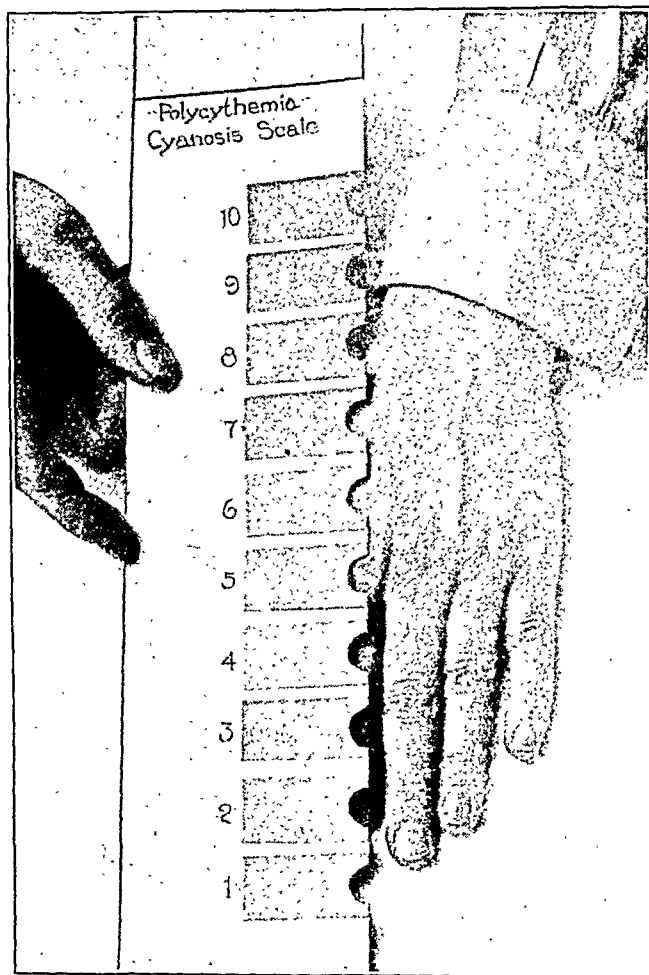


FIG. 3.—Individual color scales as employed in the routine measurements of skin color.

the color plaques were subjected to analysis by the Munsell method of color measurement³ (Fig. 2).

The routine method in our clinical work has been comparison of

³ The Munsell system of color measurement employs a series of color disks with perforations and slits allowing disks to be superimposed exposing various segments. Color is measured according to hue, value and chroma. The color measurements according to hue, value and chroma are printed on the back of each disk. A small motor is employed with a cardboard disk of neutral gray. The circumference of the disk is divided into degrees. Disks of selected colors are placed on motor shaft and spun. Changes in disks and in the amount of exposure are carried out until accurate matching is obtained (Fig. 4). Complete instructions are supplied by the Munsell Color Company, 461 Eighth Avenue, New York City.

the skin with separate color scales or tintometer (Fig. 3). The readings have been recorded in terms of the number of the plaque.

These plaques have all been subjected to color analyses according to hue, value and chroma (Fig. 4). In many instances color

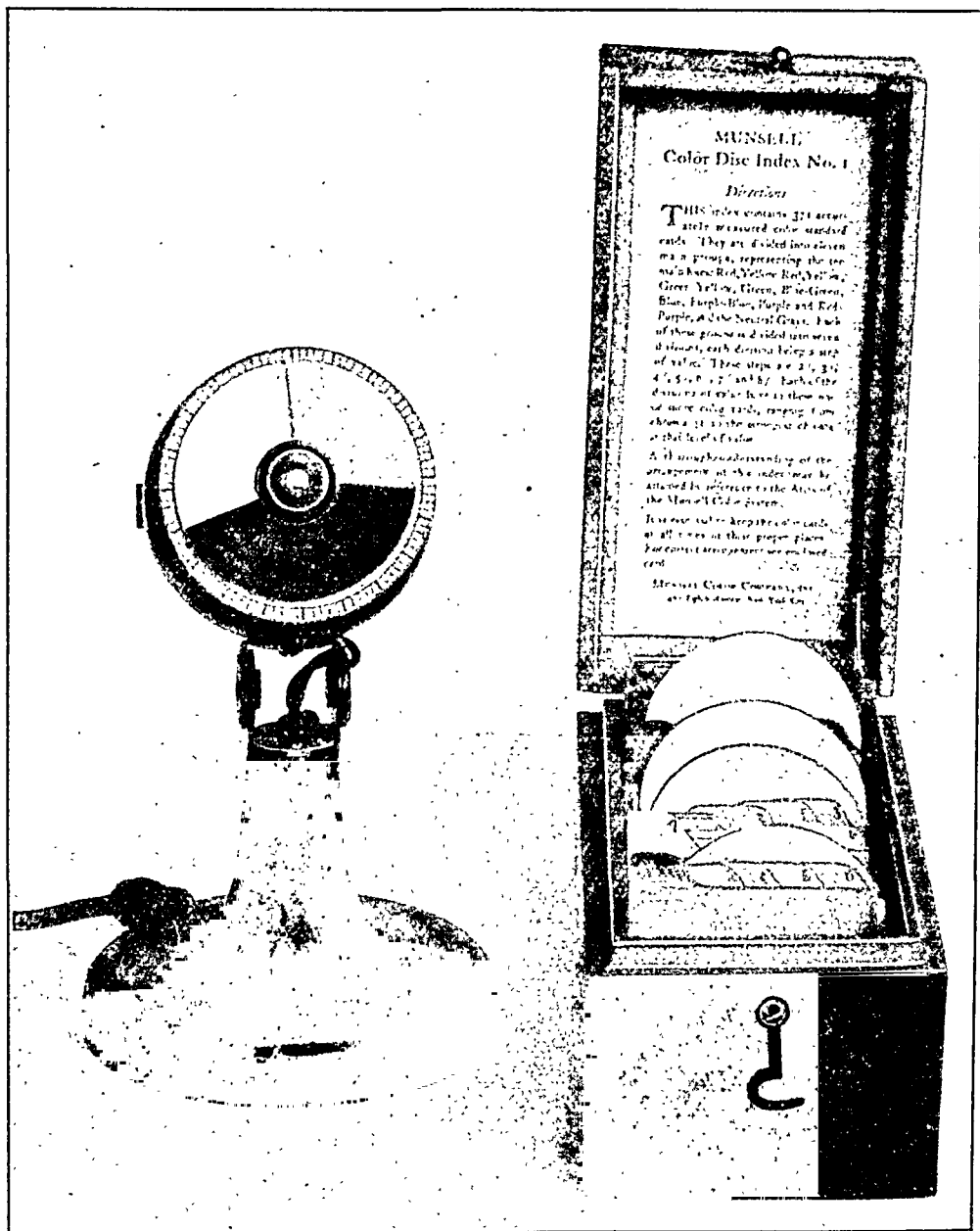


FIG. 4.—Reproduction of the Munsell color disk index. Each color card has its measurements according to hue, value and chroma. These are placed on the disk on motor shaft and spun.

measurements were made by direct comparison of the spinning Munsell disks with the skin, and the formula recorded for future reference. Subsequently, color patches were made at will by reassembling the color disks according to the formula. Repeated comparisons indicate the degrees of color change.

The Range of Error of the Method. Studies under controlled conditions as to light, posture and temperature involving reproductions of skin color by various members of the art staff have shown maximal differences approximating 15 per cent. Similar controls involving direct comparisons of the skin with spinning Munsell disks, made both by trained and untrained observers, have shown a range of error of about 20 per cent. From this it would appear that matching of the color of the skin is difficult but that these methods, although subject to considerable error, are still infinitely better than the usual clinical description.

In determining and ascertaining the color of the skin it is the gross effect rather than the detailed color which one considers. Exact comparison of flat colors with the multiple hues seen in the detailed color of the skin is impossible. This difficulty is probably greater in the study of normal skin than it is in skin markedly pigmented. The normal skin colors are a complex mixture, comprising yellow, green, blue and red, as shown in the Munsell analysis. The skin capillaries and venules contribute the red and blue factors, while the skin itself is a mixture of green and yellow. Temperature exerts a very definite effect on color as well as the position of the part in relation to heart level. The color values vary markedly in different areas of skin in the same individual. Psychic and nervous factors at times also play a striking part.

Summary. From a large number of plaques representing artists' reproductions of skin color from approximately 100 normal and pathologic subjects a tintometer has been constructed which apparently covers adequately the entire range of color variations encountered in human skin in health and disease. The tintometer consists of multiple color scales, each composed of ten plaques, representing progressive increase in color, each plaque of which has been analyzed qualitatively and quantitatively and expressed in three dimensions of hue, value and chroma. The normal range of variations has been first determined. A separate color scale has been constructed for jaundice, cyanosis, erythrosis and brown pigmentations, each resembling somewhat the Tallqvist scale employed in the clinical determination of hemoglobin. By means of these tintometers direct comparisons with the color of the skin are made.

While the method is subject to considerable error, it offers marked advantages over the usual clinical descriptive method. The colors can be readily and accurately duplicated and new tintometer scales constructed at will through the aid of the Munsell apparatus.

Further work is in progress directed toward simplification of the method and also toward the development of a spectrophotometer method which will permit direct reading of the skin. This preliminary report is presented in the hope of indicating the need of a clinical method for accurately defining skin color and of stimulating further interest in this type of work.

GIARDIASIS: ITS FREQUENCY, RECOGNITION, TREATMENT AND CERTAIN CLINICAL FACTORS.*

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NOTWITHSTANDING many recent medical papers on this subject, Giardiasis enterica deserves more thorough clinical investigation. Considered by many a harmless intestinal parasite, recent investigation indicates that it may have a real pathogenicity.

This flagellate was discovered in 1859 by Lambl,⁶⁵ and often bears his name, although he erroneously thought it belonged to the genus *Cercomonas*. Grassi,^{38, 38a, 38b} in 1877, described the same organism under the name of *Dimorphus muris*, and two years later renamed it *Megastoma entericum*. Bütschli,^{15a} in 1886, again changed its name to *Megastoma intestinalis*, which Stiles,¹⁰⁶ in 1902, changed to *Lamblia duodenalis*. Kofoed,⁵⁷ in 1915, first proposed the name *Giardia lamblia stiles*, which he again changed to *Giardia enterica* (1920), since it was found to correspond to a flagellate originally described in tadpoles and so classified by Künstler⁶² in 1882. Excellent résumés, together with biologic investigation of this many-named intestinal parasite, can be found in papers by Charles E. Simon^{100, 101} and by Hegner.⁴²

Hemmeter⁴⁴ observed and put on record (May, 1902) the first American case infected with this parasite and our interest in this subject dates from his report before the American Gastroenterological Association in May, 1920. Immediately after this meeting one of us (B. B. V. L.) found a duodenal aspirate swarming with the vegetative form of this parasite. Since then among 798 patients examined intraduodenally we have seen 31 cases, 20 of whom were studied and 15 were treated. In all of the cases the *Giardiæ* were first recognized in the living state during the duodenobiliary drainage. The morphology of this parasite is well described by Simon¹⁰⁰ and others. Their appearance and behavior (under high-power lens) in duodenal aspirates has been described by one of us.⁷⁴

The purpose of this paper is to direct attention chiefly to three points: (1) The relatively increased frequency of this infection in temperate zones; (2) its clinical association with gall-tract disease; (3) its unusual stubbornness to all forms of treatment.

Occurrence in Temperate Climates. Until recently Giardiasis enterica has generally been considered a parasitic infestation of

* Read before the American Gastroenterological Association, May 25, 1925.

only tropical or subtropical zones. More recent work indicates its greatly increased recognition in temperate climates. In reviewing current literature since 1912 we find records of 3200 cases in which either the vegetative flagellates or their cysts were recognized. Chart I records the various cases reviewed. Of this total number, 1500 were reported by Musgrave⁸⁵ from his Philippine records and might justifiably be excluded from the temperate zone group. Kofoid and others⁸⁶ found 900 cases among 15,000 apparently healthy American soldiers. The third largest series was reported by Fanthem and Porter,³⁵ who found 187 cases among 1300 patients with diarrhea. Chart I shows that by far the largest recognition of this parasite has occurred by finding the encysted forms in stools examined with Donaldson's eosin and iodine stain.

CHART I.—TOTAL NUMBER OF CASES REVIEWED (ARRANGED ACCORDING TO NUMBER OF CASES).

	No. of cases of giardiasis.	Recognized by duodenal aspirates.	Recognized by cysts in stools.
Musgrave, San Francisco, 1922	1500	..	1500
Kofoid, <i>et al.</i> , California, 1919	900	..	900
Fanthem and Porter, Great Britain, 1916	187	..	187
Willis, Australia, 1923	84	..	84
Matthews and Smith, Liverpool, 1921	77	..	77
Castex and Greenway, Buenos Aires, 1925	70	4	66
Logan and Sanford, Mayo Clinic, 1917	66	..	66
Cheney, California, 1922	34	..	34
Le Noir and Deschien, Paris, 1924	30	..	30
Reed and Wycoff, California, 1922 and 1924	22	..	22
Woodcock and Penfold, England, 1918	22	..	22
Maxcy, Baltimore, 1921	17	..	17
Hemmeter, Baltimore, 1920	12	..	12
Kennedy and Rosewarne, England, 1916	12	..	12
Simon, S. H., New Orleans, 1922	10	3	7
Kingston, Louisiana, 1922	10	10	
Hollander, New York City, 1923	9	9	
Dionnet, France, 1923	9	..	9
McGill, Montana, 1922	9	..	9
Levin, New Orleans, 1918	6	..	6
Tsuchiya, Battle Creek, Mich.	6	..	6
Smithies, Chicago, 1918	5	..	5
Jeffrey, Michigan, 1925	5	1	4
Simon, C. E., Baltimore, 1922	5	..	5
Lyon, Indiana, 1919	2	..	2
Rodenwaldt, Poland, 1912	2	..	2
Lucas, Kentucky, 1922	2	..	2
Silverman, New Orleans, 1922	2	2	
Raue, Germany, 1923	1	..	1
Kantor, New York, 1923.	1	1	
Additional unpublished cases of giardiasis (Lyon and Swalm)	20	20	
By personal communication with Phila- delphia group of doctors	63	41	22
	<hr/> 3200	<hr/> 91	<hr/> 3089

Since the inception and wider application of duodenobiliary drainage as a diagnostic procedure, the incidence of recovery of

the living vegetative forms has greatly increased. Since 1922 a total of 91 cases has been reported in the literature in which the *Giardiæ* have been recovered from the duodenal aspirates. In 1923 one of us (B. B. V. L.) mentioned 11 such instances in patients, only 1 of whom had ever been in tropical or subtropical climates. In order to ascertain the frequency of this infection among residents of Pennsylvania and neighboring states, a questionnaire was addressed to Philadelphia doctors, who make routine use of the duodenal tube. The replies indicate a surprisingly increased recognition of this parasite in duodenal aspirates, as follows: M. E. Rehfuß, 12; H. L. Bockus, 12; M. M. Rothman, 10; H. J. Bartle, 3; H. M. Eberhard, 2; J. Q. Thomas and S. Immerman, 1 each; a total of 41 cases. Furthermore, through the courtesy of Drs. Noone, Usher and Waltz; we have learned that they have observed 14 cases at the Children's Hospital in Philadelphia within the last four months in children between two and six years of age. During 1924 8 additional cases were recognized, all occurring in the last quarter of the year. They attribute the increased incidence of recognition to a more careful search for this parasite, recently inaugurated in routine stool work. No duodenal intubations were done. In the majority of their cases the diagnosis was also made accidentally, some of the cases coming through out-patient services and others admitted to the wards with pneumonia, or other acute infections which masked any definite clinical symptoms of Giardiasis. Among their group of children, diarrhea, while conspicuous, occurred in only 7 cases. Other symptoms consisted of nausea, vomiting, restlessness and insomnia. One had convulsions. This series of cases, together with our own, reaches a total of 83 cases observed in Philadelphia by a small group of doctors. The incidence is no doubt much larger, many cases not being reported and many more escaping recognition. Obviously, this infection in temperate climates is of some importance.

Method of Dissemination of Giardiasis. There is much evidence that Giardiasis is transmitted chiefly by the cysts, which are very resistant and may be eliminated for years by individuals who are symptom-free and apparently cured. Grassi successfully inoculated himself by ingesting the cysts. As in typhoid, so in giardiasis, fingers, food and flies are the chief offenders. Galli Valerio and Stiles have both shown that the house fly may carry and deposit the cysts. This may account for the small epidemic in the Children's Hospital mentioned above, which occurred in the fall and winter months.

Various rodents have been suspected of spreading the infection, but Simon, who has extensively studied this question,¹⁰⁰ believes that human infestation is of human origin, and he seems to have established specific differences existing between human *Giardiæ* and those of the house and meadow mouse. Culture rats and wild

rats cannot be infected. He believes that there is no basis for the assumption that human infection is referable to rats and mice. So too, Hegner⁴³ believes that the rabbit and cat are parasitized by a species distinct from that living in man.

Musgrave⁸⁵ points out that air-borne dust containing cysts, settling on vegetables, cereals, fruits and other foods exposed to the air, may serve as a means of dissemination. This also may apply to small water courses, shallow wells or contaminated springs, as mentioned by Smithies.¹⁰⁴

The likelihood of such methods of-transmission is suggested by the fact that in children particularly, several members of the family, may become simultaneously infected. It is possible that by air-borne routes the respiratory tract may be invaded, for *Giardia* cysts have been found in bronchiectatic secretions. In 3 cases observed by Bartle (personal communication) all had chronic bronchitis. The great increase in this infection noted during the World War among returning troops lends color to the belief that direct contact with dejecta and generally unhygienic living conditions tend to spread the disease.

Pathogenicity. Can such intestinal parasites be responsible in part for many obscure gastrointestinal disorders? The consensus of more recent opinion is in favor of this point of view, and our experience reported herewith, is in accord.

From a review of our cases we believe that *Giardiæ* may constitute a contributing factor to a state of disease or dysfunction particularly involving the gall tract, the duodenum and jejunum. Very little seems to be known as to why this parasite apparently elects its chief localization in the duodenum and jejunum. By its peculiar sucker-like peristome it attaches itself to the duodenal epithelium and even penetrates within the deeper glandular layers, and so distorts the duodenal cells as to be readily recognizable by microscopic examination of fresh aspirates. This injury to the duodenal mucous membrane has also been noted at autopsy by Galli Valerio.¹¹¹

It is our opinion that such constant irritation of the duodenum seems capable of producing a catarrh, and possibly an inflammatory edema, and if excessive in the neighborhood of the ampulla might produce a mechanical obstruction of bile, with a catarrhal form of jaundice. Indeed, it is conceivable that the bodies of the *Giardiæ* swarming in the duodenum in uncounted millions may of themselves produce such mechanical obstruction of the common duct. It is considered by some¹⁰² that the *Giardiæ*, with the whip-like movement of their flagella, may favor the introduction of bacteria into the common ducts, and initiate an ascending infection. Microscopy of duodenal aspirates definitely indicates that a pronounced duodenitis exists in many cases. This may be an associated factor in the production of duodenal ulcer, as observed in 1

of our cases. It has been found that their presence interferes with the proper elaboration of the succus entericus of the duodenum and jejunum. Whether this is cause or effect cannot be definitely stated, either from the evidence we have reviewed or from our personal observation.

We have been particularly interested in the clinical association of Giardiasis and gall-tract disease. Among our 20 cases, 18 of them had disease of the biliary tract, 14 of them had infected bile, 12 had definite catarrh and exfoliation and 7 suggested gall stones, proved by operation. Four were jaundiced and 6 showed evidence of diminished pancreatic function, 1 patient having a tumor of the pancreatic head. That this is not an uncommon experience is indicated by a review of recent literature in which the association with gall-tract disease is mentioned by Smithies, Knighton, Silverman and Kantor, and by personal communication from Rehfuß, Bockus, Eberhard, Rothman and Bartle. However, the frequency of association with gall-tract disease cannot be very great, since we have been able to demonstrate Giardiasis in only 20 out of 798 patients in whom duodenal aspirates were carefully studied, and in whom various types of gall-tract disease was recognizable in approximately 80 per cent.

Do the *Giardiæ* Invade the Gall Bladder or Bile Ducts? In connection with its relation to gall-tract disease, a most interesting point, as yet unproved, is whether the *Giardiæ* themselves do actually invade the gall bladder. We have not been able to trace any single authenticated instance. Throughout the literature this finding has been attributed to Smithies on account of his verbal discussion of Hemmeter's paper in 1920.⁴⁴ Reviewing Smithies' own contribution¹⁰⁴ to which he referred in that discussion, we find it concerned a study of 1000 patients among whom were found 93 cases of protozoal infection, 5 of which were *Giardia*. Although Smithies states "Our studies of specimens in gall bladders and appendices removed at laparotomy indicates that in these parts of the gut cysts of protozoa may lurk for years," yet there is *no specific statement* in that paper that *Giardiæ* themselves were found in any gall bladder. It has been taken for granted through the ensuing literature that this is a fact.

In 2 reported cases in which the gall bladder was diligently searched for *Giardia*, they were not found. Silverman¹⁰² states: "We found the same character of bile as was recovered by the duodenal route, but while the latter contained myriads of *Giardiæ*, neither did the gall-bladder mucosa nor its contents reveal any of the parasites or their cysts." In a second case reported by one of us,⁷⁴ in whose duodenum numerous *Giardiæ* were found, at a later operation no *Giardiæ* were found either in gall-bladder bile or scrapings from the mucous membrane of a gall bladder containing 155 stones. However, it is interesting to note that in this particular case, three

years later, studies of stools after brisk purging failed to demonstrate either flagellate or encysted forms.

There is considerable *clinical* evidence, however, that infestation of the gall bladder or ducts is a possibility. We and others have noted patients relapsing under various forms of treatment, in whom for weeks or months *Giardiæ* could not be demonstrated in duodenobiliary aspirates; then they suddenly appeared, conspicuously and in several instances, exclusively in the "B" or gall-bladder fraction. This occurred in 5 of our own patients, and in several seen by Bockus (personal communication) and in 1 by Knighton.⁵²

The latter assumes that his case had an infestation within the gall bladder and believes that reinfestation took place in the duodenum from this source, since he could find parasites only in the centrifuged "B" fraction after magnesium sulphate stimulation. He says: "If there is any doubt as to *Lambliæ intestinalis* infecting the bile passages, this should settle the question."

Symptoms. Except during the acute period of infection, when there is often diarrhea (especially in children) there does not seem to be any definite symptomatic picture which can be ascribed to Giardiasis. There may be vague or definite symptoms of the gall bladder ulcer group, as mentioned by Cheney,²⁴ McGill⁸¹ and noted frequently in our cases. Cheney suspects Giardiasis in all chronic cases of an indefinite type, particularly those with added nervous symptoms, "all gone" sensation and irritable intestines. Sidney Simon,¹⁰² in 8 cases, quite frequently found increased abdominal gas and abdominal cramp-like distress, but believes that no one symptom or group of symptoms is a reliable diagnostic sign, but a suspicion of Giardiasis should be entertained in all cases of indefinite diarrhea and increased abdominal gas. Galli Valerio¹¹ observed in all of his cases alternating constipation and diarrhea with general depression, pale skin and mucous membranes. Among his cases true dysentery did not occur.

Through the courtesy of Profs. M. R. Castex and D. Greenway, of the Faculty of the University of Buenos Aires, we have received the following notes from a paper shortly to be published in the *Prensa medica argentina*. In a study of 614 cases²¹ these authors observed 70 instances of Giardiasis associated with other protozoal parasites. In 4 cases they demonstrated the *Giardiæ* during duodenobiliary drainage. It reached 11 per cent of their parasitic findings and occupied the fifth place in their parasitological studies. Among the clinical symptoms they found in some cases high-grade constipation with spontaneous evacuations every second or third day, improved only by proper diet. In other cases constipation alternated with diarrhetic episodes, with abdominal colic, tenesmus and abundant mucus. In some of the constipated patients laxatives provoked acute enterocolitis with anxious state of feeling, and intensified the toxemic symptoms. Anorexia, nausea, pyrosis,

regurgitation, vomiting, gastric discomfort, abdominal distention and acute pain in the right upper abdomen occurred most frequently in their patients. Diffuse abdominal pain or pressure and more or less enlargement of the liver was found in many of them. Headache, physical and mental weakness, paresthesias, agripnias, neuralgias and general toxemic symptoms are emphasized by these authors.

Discussion of Symptoms in Our 20 Cases. (Chart II.) *State of Bowels.* With the exception of 1 patient, all of our last 20 cases, now reported, occurred among adults. There were 9 females and 11 males. Although diarrhea seems to be a symptom commonly mentioned in the literature, it is far more frequent among children. It would appear that this parasite when chronically implanted is more apt to be associated with constipation. Twelve of our cases had definite constipation, 5 very obstinately; 5 had normal bowel function and only 3 diarrhea. In 1, a boy, aged eleven years, the diarrhea appeared due to Giardia, and represented a freshly acquired infection. Of the other 2, 1 had gastric anacidity, with associated pancreatitis and the other intestinal tuberculosis, which might account equally well for the diarrhea. Therefore, in our personal experience with the adult form a state of diarrhea has been unusual. In our group of patients the Giardia was the only intestinal parasite encountered, although it has been commonly found by other observers to be associated with entameba, trichomonas, chilomastix, blastocystis hominis and other parasites. Among the American cases the majority of these mixed infections have been reported by doctors living on our southern and western coasts, where intestinal parasitic infections are more common.

Pain. Abdominal pain, occurring in 14 cases, was usually noted in the upper abdomen, more often in the right upper quadrant. It varied from a vague pain distress to definite generalized cramps in 1 case of active diarrhea. Some patients complained of an "all gone" sensation, not unlike a hunger pain.

Other Digestive Symptoms. Abdominal distention was a common finding, with belching noted in 12 cases and flatulency in 11. Nausea occurred in 6, with vomiting of a biliary type in only 1 case. Nine had intestinal stasis, as evidenced by the carmine test meal and barium progress meal.

Toxic Symptoms. Headache occurred in 11 cases; it approached in severity the biliary migraine type in 5. Dizziness was complained of by 6 of these patients, 4 to a mild extent. One patient noticed it especially on suddenly lying down, getting up or turning quickly. One patient had definite vertigo, falling on the street on several occasions. In 7 cases the clinical picture suggested hepatic intestinal toxemia, although indicanuria was present in only 5. Seven patients had ill-defined, but definitely increased, restless nervousness.

Other Symptoms. Twelve patients complained of moderate to severe weakness. Cardiac palpitation was noted in 8 patients and 3 associated with myocarditis. One patient had many fainting attacks after the evening meal, and was particularly intolerant to alcohol and tobacco. Loss of weight was conspicuous in 8 patients, ranging between 8 and 39 pounds. Enuresis or priapism was noted in 3 instances. In 3 cases there was an associated arthritis, in 2 of whom it took the hypertrophic variety with much deforming of hands and feet, and a noticeable soft periarticular swelling. The third case fell into the Paget's group. In all 3 there was a noticeable whiteness of the skin and mucous membrane, due to anemia.

Many of the above group of symptoms were very promptly relieved after instituting appropriate treatment. After reviewing the symptoms occurring in our cases, one is left with an uncomfortable feeling of uncertainty as to whether they too may not have occurred in spite of, rather than because of, the *Giardiæ*.

Laboratory Studies (Chart II). It has been stated that *Giardiæ* are intolerant to hydrochloric acid and that they might therefore more frequently occur in cases in which gastric acidity is lowered. Our experience, however, does not confirm this. In 15 of the 20 cases in whom fractional analyses were recorded, 8 showed definite hyperacidity, 3 normal acidity, 3 subacidity and only 1 anacidity.

In 19 of the 20 cases occult blood to benzidin was tested in the stomach contents, duodenal contents and stools. In 12 instances it was +1 to +2 in the stomach; in 7 patients, +1 to +2 in the stools; in 3 patients, +1 in the duodenal contents. In 2 of the latter instances there was definite duodenal ulceration. This comparatively infrequent finding in the stools is in contrast to the more frequent bleeding from the intestinal tract infected with *Entameba histolytica*. In no instance was there gross blood recognizable in the stool.

In no patient was there anything distinctive in urinalysis, only 5 instances of indicanuria being observed among 20 cases.

There was definitely decreased pancreatic enzyme activity in 6 patients. In this connection other observers have noted that the size of the stool is apt to be large and greasy when no diarrhea is present. This was not noted in our cases.

The blood count seems to indicate a distinct tendency to anemia and a slight leukopenia with relative lymphocytosis. In 14 cases complete blood counts were done one or more times, and in 9 of these the hemoglobin ranged between 57 and 82 per cent and averaged 68 per cent; the leukocyte counts ranged between 4600 and 8800, with an average of 6300; lymphocytes between 13 and 53 per cent, with an average of 29 per cent; the eosinophilia was noted in only 8 of the 14 cases, in no instance went above 4 per cent and averaged for the group a normal 1.3 per cent. Absence of noteworthy eosinophilia therefore seems to distinguish this infection from other forms of parasitism.

CHART II

Case. No.	Age.	Sex.	Duodenal vegetative forms.		Cysts in stools.	Constipation.	Diarrhea.	Normal bowel function.	Colitis.	Enterocolitis.	Pancreatitis.	Associated with gt. disease.	Gall Tract infection.	Gall Tract catarrh.	Gall stones.	Jaundice.	More in "B" than "D" bile.	Relapsing from "B."	Static "B" bile.	Associated with App'x. dis.	Pyloro-duod. ulcer.	Duodenitis.	Gastric acidity.	Associated with arthritis.
I	11	M.	+	+	..	+	+	..	+	Sta. aur. vac.	+	+	+	Hyper.	..
II	30	M.	+	+	+	+	B. coli; no vac.	+	Out	Normal	..
III	48	F.	+	+	+	+	+	Sta. aur.	+	+	+	Hyper.	+
IV	39	M.	+	+	+	+	+	+	..	+	+	+
V	59	M.	+	+	+	?	B. coli vac.	+	+	+	+	Sub.	+
VI	50	F.	+	+	..	+	..	+	..	+	+	Sta. aur., nonhem. st., oper.	+	+	+	An acid	..
VII	49	F.	+	+	+	+	..	+	+	Sta. aur.; B. coli vac.	+	+	+	+	+	Sub.	..
VIII	35	F.	+	+	..	+	..	+	+	Not cult.												
IX	59	F.	+	+	+	+	Hem. st., sta. aur. vac.	+	?	+	+	Hyper.	..	
X	68	M.	+	..	+	+	..	+	+	Not cult.	+	+
XI	33	M.	+	..	+	+	+	?	+	+	..	+	+	+	+	+	Hyper.	..
XII	25	F.	+	..	+	..	+	Now	+	St. nonhem.	+	Out	..	+	Normal	..
XIII	43	F.	+	..	+	+	+	+	+	..	+	Out	..	+	Normal	..
XIV	20	F.	+	+	Sterile	+	Hyper.	..
XV	39	F.	+	..	+	+	Sta. aur., nonhem. st. vac.	+	+	..	+	Out	..	+	Hyper.	..
XVI	40	M.	+	..	+	+	+	Sta. aur., no vac.	+	?	+	+	+	+	Sub.	..
XVII	57	M.	+	+	+	+	+	?	+	+	+	Out	..	+	Hyper.	..
XVIII	21	F.	+	..	+	+	+	+ nonhem. st., Sta. aur.	+	?	+	+	Mod. hyper.	..
XIX	56	M.	+	+	?	+	+	+
XX	50	F.	+	..	+	+	+ B. coli	+	+	+
Totals	20	9	12	3	5	6	2	5	18	14	12	..	4	9	5	14	2	2	15	8 hyper. 3 nor. 3 sub.	3	

CHART II.

Abdominal pains, distress.	Belching.	Flatulency.	Nausea.	Headache.	Dizziness.	Increasing nerv's.	Weakness.	Palpitation or cardiac.	Enuresis-priapism.	Hepatic intest. toxemia.	Indicanuria.	Intest. stasis.	Loss of weight.	Hemoglobin, per cent.	Leukocytes, thousands.	Lymphocytes, per cent.	Eosinophilia, percent.	Duration of observation, mos.	Occult blood.		
																			Stomach.	Duodenum.	Stools.
Cramps	+	+	..	+	85	5.6	41	..	30 mos.	+	..	+ ²
All gone	+	+	..	+ ⁴ ; bil. migr.	+	+; fainting eve.	+	+	95	..	17	..	9 mos.	+		
Low abd. and gas	+	+	+	+ ⁴ ; bil. migr.	+	+	..	+	..	+	..	73	5.9 5.2 6.8 7.6	13 to 27	1 to 4	10 mos.			
Up. rt. q.	+	+	..	Bil. migr. sev.	+														
...	..	+	+	65	..	21	..	6 mos.	+		
Epigast.	+	+	..	+	+	+	+	+	+ 39 lbs., 1 yr.	82	4.7	30	1	1 mo.	+ ²	..	+
High epigast. of up. r. q.	+	+	+	+	+	+	..	+	+ ²	97 88	..	25	..	4 mos.	+	+	+
Up. r. q.; low r. q.	..	+	+	+	+	+	+ 8 lbs., 6 mos.	70	6.0	53	1	+		
.....	+	+	57 60	4.6 5.5	13 7	1 1				
Midepi. gast. gas	+	Bil. migr.	+	..	68 to 78	5.7 6.4 7.2	33 43 19	2 3 3	15 mos.	+	+	+
Up. r. qt. attacks	+	+ ³	+	+	+	+	..	+	..	65	6.2	37	2	+	..	+ ²
Up. r. qt. sore.	+	Bil. migr.	+	+	+	+ myocardial weak.	70	4.6	19	3	12 mos., by letter	+	..	+ ²
.....	+		
.....	+	+	+	..	+	+	..	Occas.	..	+	+	+	+	78	5.8	29	..	6 mos.			
Gen. abd. distress	+	+	+	..	+	+	+	+ dysp.	..	+	..	+	+ 14 lbs., 6 mos.								
+	+	+	+	+	..	+ freq.	10 mos.	+	+	
.....	+	+	+	+	+	+	5 mos.			
.....	+	+	+	+ ²	+	..	+ ²	+ 9 lbs., 1 yr.	30 mos.			
.....	+	+	12 mos., ca 34 drain.			
14	12	11	6	11	6	7	12	8	3	7	5	9	8	12	3	7

Treatment. A review of the literature of Giardiasis brings out prominently the fact that this parasite is by comparison with many others remarkably resistant to treatment. It is highly probable that as yet no specific treatment has been developed. The following drugs in various dosage, either alone or in combination, have been tried: Tannic acid, ichthyol, hexamethylenamin, methyl blue, dilute hydrochloric acid, beta-naphthol, thymol, bismuth salicylate or subnitrate, guaiacol carbonate, turpentine, salol, quinin, sulphur, copper arsenite, Chaparro amargoso, calcined magnesia, soda bicarbonate, castor oil, calomel, santonin, emetin, ipecac and arsphenamin.

Various writers have recorded cures, particularly with thymol, hexamethylenamin and arsphenamin, but the duration of observation of many of these cases was hardly long enough to make such claims valid in view of the notable tendency of relapse. As long as any single parasite is left behind, repropagation seems possible. In 1917 Yakimoff¹¹⁸ found that arsphenamin was extremely effective in white mice. This was confirmed by Kofoed,⁵⁵ in 1918, who experimented on rats. Afterward its use was applied in human beings with perhaps the largest measure of success attributed to any drug. It must be given in full doses, inasmuch as small initial doses seem merely to stun the parasite and develop in it a tolerance for the drug.

In the small epidemic of 22 cases observed at the Children's Hospital of Philadelphia treatment was attempted in approximately 30 per cent. Thymol and hexamethylenamin were without effect. In 4 cases sulpharsphenamin was used intramuscularly without appreciable result. One case, three years of age, received four large doses, one injection of 2 dg. and three of 3 dg., and still continued to relapse. Temporary improvement could be secured, but relapses occurred.

One or two writers have used arsphenamin intraduodenally, and have noted improvement.

It is very important, however, in reviewing treatment of this disease, to definitely separate clinical improvement from parasitological cure. Castex and Greenway, of Buenos Aires (personal communication) state: "We tried without any result the use of thymol, calomel, turpentin, quinin, methyl blue, sulphur, arsphenamin, bismuth salicylate, beta-naphthol and guaiacol compound. We have not the same enthusiasm for arsphenamin that the American authors have, having given it intravenously in full doses with no appreciable final results. In our hands the two best remedies have proved to be the French stovarsal Poulenc and the German yatren 105 Behring." They precede treatment with the use of cholagogues or biliary extracts and by repeating or alternating this treatment, obtain excellent results and could free patients of their Giardiasis, generally in one or two months. Treatment with stovarsal Poulenc

was carried out in the following way. For three days, 3 tablets of 0.25 gm. a day, three days' rest; 3 tablets of 0.25 gm. for three days, then fifteen days' rest. If the stool still contains *Giardia* cysts stovarsal is repeated a second time. If no cysts were found bile extracts were given for five days and stools reexamined. With yatren 105 Behring the treatment was carried out as follows: For ten days 3 cachets daily of 0.75 or 1 gm., then ten days' rest. Examination of the stools and according to the result, the yatren was repeated one or more times. In their hands yatren gave the best results.

Our Own Therapeutic Experience. In our own experience, because the majority of our cases were associated with gall-tract disease, we relied partly on the effect of biliary drainage with magnesium sulphate intraduodenally. This drug seems to have great power in stunning or inhibiting the movement of *Giardiæ*, many millions of amotile forms being subsequently washed out of the duodenum from time to time. In continued usage it may be more potent than we think for *Giardiæ* within the duodenum and jejunum, but has no power to attack the parasite if lodged in the biliary channels. We have noted the parasite suddenly reappearing after intervals of absence running into months, and as previously stated in 5 instances recognized only in the gall-bladder fraction bile.

The same opinion may be expressed in regard to dimol, a phenol derivative, with which we have experimented with variable results. In 1 of our 2 cases in which we believe a cure might be claimed dimol was the only drug in addition to magnesium sulphate with biliary drainage, that was used.

In Case I ten weekly drainages were given, followed each time by transduodenal lavage with 500 cc of 1 per cent dimol. Although originally present in great abundance, no *Giardiæ* were found after the second treatment, although rechecked on the fourteenth day, and thereafter at weekly intervals for three months. The diarrhea in this boy, aged eleven years, was promptly controlled and was therefore assumed to be due to the *Giardia*. There was general symptomatic improvement and a gain in weight of from 79 to 102 pounds, in thirty months. On a final recheck made twenty months after discontinuing treatment, we could find no vegetative forms in the duodenum and no cysts in the stools after brisk purging.

Our second apparent cure occurred in Case XIII. A woman, aged forty-three years, was given thirteen biliary drainages, twelve instillations of 100 cc of 2 to 4 per cent dimol, in sterile water, to a total of $8\frac{1}{2}$ dr. In addition, neoarsphenamin was used intraduodenally on the fifth and tenth days, in dosage of 0.3 to 0.45 gm. The *Giardia* disappeared after five drainages, the fourth dimol and the first intraduodenal neoarsphenamin. The drainages were then continued for about eighteen months at monthly intervals, and at no time thereafter were *Giardiæ* again detected. Marked general

improvement was secured and a gain of weight from 96 to 106 pounds.

That it is unwise prematurely to credit the effectiveness of any drug in a condition as stubborn to treatment as Giardiasis, is evidenced by Case XVII, a man, aged fifty-nine years, who was given twenty-four drainages, twenty-four dimol instillations in 1 per cent solution and one intravenous neoarsphenamin of 0.6 gm. The *Giardiæ* disappeared after the fourth day's treatment, but a relapse occurred six months later, although marked general improvement was secured. This patient was given dimol daily by duodenal tube for twenty-one days.

In Case V, a male, aged fifty-nine years, with hypertrophic osteoarthritis, and a possibility of focal infection in the gall bladder, the patient was given *continuous* biliary drainage for seventeen days, with a daily duodenal lavage with silvol solution, 1 to 5000, sodium iodid intravenously and hexamethylenamin by mouth. The *Giardiæ* disappeared after the eighth day of treatment, but a relapse took place two weeks after drainage was discontinued. Five years later *Giardia* cysts were found in abundance in the purged stools of this patient. Moderate improvement in the arthritis was secured.

Case VI, a female, aged fifty years, with gall stones, whose duodenum contained the vegetative forms, was not treated medically. Her gall bladder and contents were removed. No *giardiæ* were found in the gall-bladder bile or mucosal scrapings, and yet three years later careful search of liquid stools failed to demonstrate their presence. This patient has secured complete improvement.

Case XV, a female, aged thirty-nine years, observed on the first day of acute catarrhal jaundice, was found to have a pronounced duodenitis and swarming *Giardiæ*. Later drainage findings indicated an intermittent catarrhal obstruction of the cystic duct. Dizziness and lack of endurance were conspicuously complained of. There was moderate anemia, leukopenia and lymphocytosis. She was given twelve drainages, followed by twelve transduodenal lavages with Ringer's solution, eight intraduodenal instillations of silvol, 1 to 5000, and four of 2 per cent dimol. The *Giardiæ* disappeared within three weeks and have not since been detected over a period of four months. This period of observation in Giardiasis, however, is too short to be of final value, although marked general symptomatic improvement was secured.

Case XVI, a male, aged forty-two years, with pronounced symptoms of gall-tract disease and drainage findings of cholecystodochitis and suggested lithiasis, had myriads of *Giardiæ*. He has been under observation for three months, and has had nine drainages,

five transduodenal lavages of silvol, 1 to 5000, and seven of dimol, 1 to 2 per cent. The *Giardiæ* disappeared from the duodenum and remained absent for five weeks, when they reappeared in abundance but were found only in the static gall-bladder fraction bile.

Case XVIII, a female, aged twenty-one years, was given eighteen drainages followed by 2 per cent dimol, transduodenal lavage, and in addition, given dimol tablets internally by mouth, for one month; 0.9 gm. of arsphenamin was given on the third day. The *Giardiæ* disappeared after the third weekly drainage, and have not been detected since then, over a period of five months, which we believe is not sufficiently long to claim a definite cure. Marked general improvement was also secured in this case.

Case XX, a male, aged fifty years, under observation for one year, has been given thirty-four drainages at weekly intervals, 1 per cent dimol by intraduodenal lavage and two intraduodenal injections of neoarsphenamin of 0.45 and 0.6 gm. The *Giardiæ* promptly disappeared, but after three months recurred intermittently in "B" bile, in moderate numbers, in spite of weekly drainage. Neoarsphenamin by duodenum nauseated this patient and was discontinued. An autogenous vaccine of *B. coli* from bile cultures was given, with improvement. Dimol tablets were taken by mouth between drainages, but the *Giardiæ* still persisted.

The other 6 cases were of the same general character, and treated similarly, with no definite cure of the Giardiasis, relapses occurring unexpectedly after apparent early success.

From the citation of the foregoing cases it will be evident that caution must be observed in claiming a definite cure in Giardiasis. On the whole, our experience with treatment has been distinctly disappointing.

Summary. 1. Giardiasis enterica is an intestinal parasite of clinical importance, quite frequently observed in temperate climates.

2. It seems to have a definite pathogenicity and in adult patients is most often found clinically associated with disease of the gall bladder, bile ducts and duodenum.

3. It is unusually resistant to all forms of treatment. It is highly probable that as yet no specific treatment has been developed.

4. Owing to the frequency of relapses observed, caution should be exercised in prematurely claiming an actual cure in Giardiasis.

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TROPICAL SPRUE IN A CHILD SIX YEARS OF AGE.

WITH ISOLATION OF MONILIA FROM PATIENT AND TISSUES OF
INOCULATED ANIMAL.

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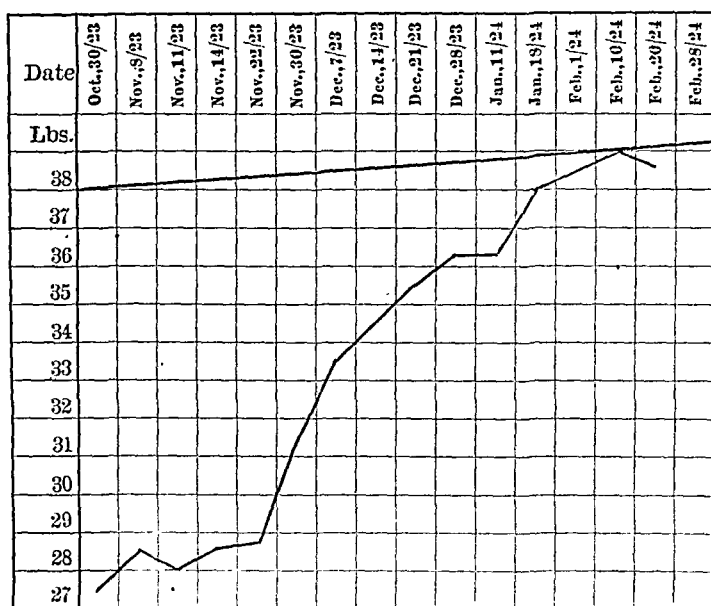
THE subject of tropical sprue has been so carefully studied by Col. Bailey K. Ashford, Medical Corps, U. S. A., and has been presented by him in Oxford Medicine in such a masterly way, that there seems very little further to be said on the subject today. Nevertheless, additional confirmation of some of his hypotheses cannot come amiss. Comparatively so few cases have been seen in the U. S. A. that it would not have been strange if we had missed a diagnosis which two of the largest schools of tropical medicine in the world had failed to make. But now we have become not only a country with tropical dependencies but also a nation of travelers, and many of our citizens now engage for shorter or longer periods in business or missions abroad and are thereby exposed to these tropical infections. We therefore need to become more familiar with their manifestations.

It is with the idea of bringing more forcibly to our attention the fact that such cases may be and are found in the U. S. A., and with the hope of familiarizing ourselves with the symptoms, clinical findings and treatment, and to present proof of the existence of the *Monilia psilosis* in tissues of the inoculated guinea pig, as shown by the microphotograph, that this case is presented.

The patient, a little girl aged six years, came under observation October 30, 1923. The family history was negative. She was a seven months' child, and for the first few months of her life there were some feeding difficulties and a prolonged attack of whooping cough which caused some delay in growth and development. However, at eighteen months she was practically normal. Shortly before she was three years of age, she went with her parents to India

for eight months. While there she had a bad infection with both seatworms and roundworms. At the age of four years the child returned to India, where she remained until recently. She was perfectly well and unusually athletic for a child until June, 1923, when she had an acute diarrhea with fever. At first there were from six to twelve stools a day. She grew very weak, lost weight, was dull and apathetic, but as a rule had no pain.

After failure to conquer the diarrhea at home she was sent to a famous school of tropical medicine for study and observation, where roentgen-ray examination and extensive microscopical and bacteriological studies were made, with a final conclusion that the disease was due to a chronic dilatation of the large intestine (Hirschsprung's disease). She lost weight progressively while in hospital.



Weight chart.

Stools alternated between constipation and diarrhea. Failing to improve, the mother started home with the child, weighing then 25½ pounds. Further studies were made of the case in London, with the opinion that the case was tuberculous, though no tubercle bacilli were found on eight examinations of the stools.

On entrance here the child presented the following picture: Marked emaciation and asthenia. She came in a wheel chair; could support her weight, but was very weak and did not walk. Her skin was pale, her muscles soft and flabby. Her height was 40.3 inches; weight 27½ pounds; pulse 114; temperature 97.4. Her pupils were regular, equal in outline, and responded normally to light; there were accumulations of strings of mucus under the lids. The tongue was coated. There were a few ulcers on the floor of the mouth and on the under surface of the tongue, and a marked

redness of the tip and sides of the tongue. There was excessive secretion of saliva. We were told that this ulceration healed and then recurred. Recently the teeth began to annoy with a feeling of soreness. The heart and lungs were normal, except as for such weakness as would be expected with the general malnutrition. The abdomen was greatly distended with gas. The patient was troubled for some time after every meal with marked hiccoughs. The upper margin of the liver was normal; the lower margin lay two fingers' breadth above the rib margin. The spleen was enlarged and crowded up by gas. There were slightly enlarged lymph glands, palpable in the groin, axilla and in the inner surface of the elbows. The knee reflexes were diminished. She suffered with transient pains, mostly in her legs, though occasionally in her back.

On admission she was having from one to three painless bowel movements a day, and felt relieved but exhausted after movement of the bowels. Rectal examination showed the anus spastically contracted; no ulcers or growths were palpated within the rectum. Fluoroscopical examination of the chest was negative. The urine analysis was negative. The blood count on entrance showed a mild grade of anemia; hemoglobin 75, red cells 3,610,000; white cells 8700. Differential blood count showed: Small lymphocytes, 34.5 per cent; large lymphocytes, 4 per cent; large mononuclear, 1 per cent; transitionals, 4.5 per cent; polymorphonuclears, 55 per cent, and eosinophiles, 1 per cent. There were slight variations in size and shape. The alveolar CO_2 tension was 37. The stools were unusually bulky, whitish in color, pultaceous, yeasty, foamy, and had the odor of sour, spoiled cheese. Microscopic study showed some gram-positive and gram-negative bacteria, some bacillus coli and *Monilia psilosis*.

The feces and the scrapings from the tongue of the patient were plated in ordinary laboratory media (meat infusion + 2 per cent glucose) and on Sabouraud's medium (4 per cent glucose agar, + 2 acid reaction). On the ordinary laboratory media the colonies of the yeast were highly elevated, of a white creamy color, with a slight greenish tint, while on the Sabouraud's media the colonies were the same in appearance except somewhat more glistening and of a slightly mucoid consistency. The organisms from both media fermented dextrose, levulose, maltose, and sucrose with acid and gas formation. Lactose and mannite were not fermented. There was no reaction in litmus milk. In gelatin there was a typical inverted pine-tree growth without liquefaction. Morphologically the organism isolated from the ordinary laboratory media, after five days' incubation at 37° C., resembled ordinary yeast—granular, oval, measuring from 3 to 5 microns in greatest diameter. The organisms isolated from Sabouraud's media were round instead of oval, measuring from 5 to 10 microns, having a large brilliant nucleus and a small body with the appearance of a bacillus seen to be

actively floating around the nucleus. The organisms, isolated from ordinary laboratory media, when subcultured on Sabouraud's media, resembled each other morphologically. From this it seems evident that the organisms, when grown on the above named media, seemed to be distinct entities, but when grown on Sabouraud's media, the two resembled each other culturally and morphologically. Both the organisms corresponded in every respect, when grown on Sabouraud's media, with those described by Ashford.

An agglutination test was made on the organism isolated both from the feces and tongue of the patient. The organism when brought into contact with the patient's serum failed to give a satisfactory agglutination, but neither was Ashford's culture, used as a control, satisfactory in the agglutination test. The organisms seemed to settle out and clump very quickly. The tests were carried out macroscopically and microscopically. In every instance the controls showed the same clumping as those contained in the patient's serum.

An antigen was made from the organisms isolated from the stool and tongue scrapings of the patient. This antigen was used in the complement-fixation test, with a culture of Ashford's used as control. A positive complement-fixation reaction was obtained with both. The antigen made from the organisms isolated from the patient gave a somewhat weaker reaction with the water-bath incubation technic, but gave equally as strong positive complement fixation with the eighteen-hour ice-box fixation technic (Kolmer's technic). Complement fixations were made with all the antigens, with known normal serums, without any inhibition of hemolysis.

Using water bath (37.5° C.) incubation, the antigen made from Ashford's culture gave a slightly stronger reaction than did that made from our own culture, while, on the other hand, an eighteen-hour ice-box (10° C.) incubation, using Kolmer's new technic, complete inhibition was obtained with both antigens. Control tests were made on sera from several healthy individuals with negative results.

A rabbit was injected intravenously with 1 cc of a live suspension of the organism. The rabbit died forty-eight hours after the injection with symptoms of septicemia. The postmortem examination showed multiple pyemic abscesses in both kidneys. The liver was apparently normal, the spleen normal in size and somewhat of a greenish color. The suprarenal glands were normal. Direct microscopic examination of the heart blood and smear made from the kidney showed many active *Monilia psilosis*. These organisms were reisolated from the heart blood and kidneys on Sabouraud's culture media, and were found in the tissue of the kidney, of which slides were made and photographed (Figs. 1-3).

From these cultures a vaccine was prepared for the patient according to Colonel Ashford's method.

There were three basal metabolism studies made; one, by the Talbot method, gave a + 127; a second and third, by the Aub-Dubois method, + 55 and + 39 respectively. These findings were

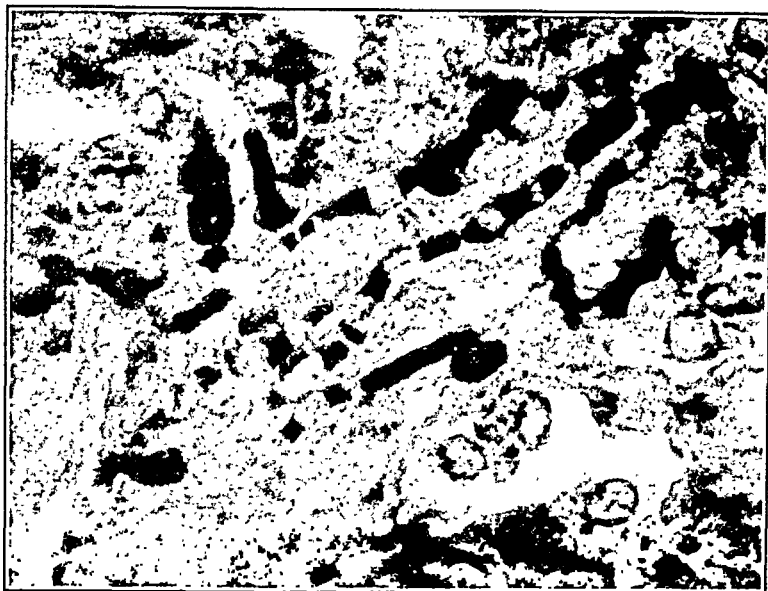


FIG. 1.—High-power microphotograph of *Monilia psilosis* as found in kidney of inoculated rabbit, autopsied.



FIG. 2.—Low-power microphotograph of *Monilia psilosis* as found in kidney of inoculated rabbit, autopsied.

calculated on the basis of several published normal standards, the lowest rate only being reported, obtained with "The Normal Standard of Talbot" based on total calories for age.

As treatment the patient was given light tonic hydrotherapy,

such as alternating heat and cold to the spine, fomentations to the abdomen, footbath, wet hand rub or cold mitten friction, and the Ohmschlag or moist abdominal bandage was worn continuously,



FIG. 3.—High-power microphotograph of *Monilia psilosis* as found in kidney of inoculated rabbit, autopsied.

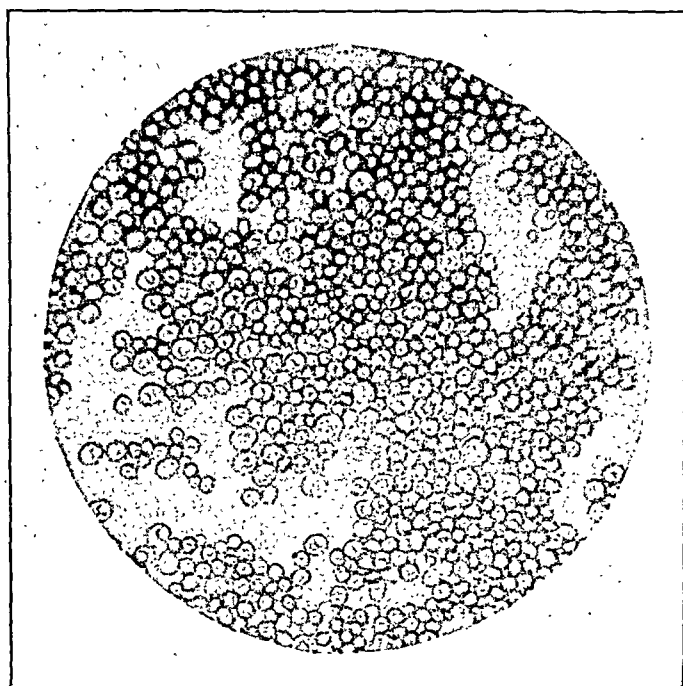


FIG. 4.—Organisms isolated from feces.

changing as often as dry. Cleansing enemas were given once a day, followed by a liquid culture of *B. Bulgaricus* and *B. acidophilus*, to retain. She was also given a culture of the same by mouth, about

3 ounces three times a day. The ulcers in the mouth were treated by applications of glycerin and phenol (2 per cent), 1 ounce of each.

She was put on a diet of acidophilus buttermilk and bananas, and after a short time was able to take a glass of buttermilk every hour and from 6 to 12 bananas a day. The bananas she took either baked or raw. The last few weeks under treatment she had some of the green leafy vegetables and an occasional baked potato, but the buttermilk and bananas still remained the principal part of her diet.

The patient was kept in bed at first, and even up to the close of her period of treatment was given two hours rest every afternoon.

During the last few weeks of treatment she was given iodine by mouth, beginning with 1 drop three times a day, increasing to 16 drops three times a day. In addition to this she was given autogenous vaccine every third day.

The child began to improve almost immediately. The bloating in the abdomen left her; she gained in weight; and the liver gradually decreased in size. Much improvement had already taken place before we succeeded in getting the vaccine made, but after a few weeks she was given the vaccine prepared and given as outlined above. She had apparently no reaction to the vaccine, but later on had localized abscesses at the seats of injection. At the close of about six months' treatment the patient had practically recovered. Her weight was 42 pounds, normal for her age. There was a proportionate gain in strength. The child previous to her illness had been very athletic, and was again doing trapeze stunts, walking and running, standing on her head, and so forth. The ulceration in the mouth came and went, healed for a few days or a few weeks, and then broke out again; but there has now been none for some months. After about three months' treatment the liver was normal in size and remained normal after that time, and the abdominal distention was very greatly diminished. At this time the stools, which were examined weekly, were still variable, though better formed and contained more bile, seldom showing the presence of the *Monilia psilosis*. The hiccoughs had been entirely controlled.

In December, eight months later, the patient had a recheck examination, and at this time we found her maintaining her normal weight, the liver normal size, very little if any abdominal distention, and the stool normal with the examination made at that time, though the mother reported still seeing an occasional characteristic stool. The last report from the mother, under date of April 19, 1925, says the stools have been brown and quite normal, and she has had no white or foamy stools since the first of January, 1925. The abdomen is still distended a little at night, but she maintains her normal weight and normal strength and activities.

Summary. A case of tropical sprue in a child, aged six years, including animal inoculation and isolation of *Monilia psilosis* both from the

patient and from the autopsied animal and photomicrographs of the parasites as stained in tissue, is reported, together with the treatment given and the results.

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THE SEVERE ANEMIAS OF PREGNANCY AND THE PUERPERIUM.

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THE occurrence of severe and often fatal anemia in pregnancy and shortly after its termination was described by Walter Channing¹ of Boston in 1842. He distinguished this form of anemia from bloodless states due to hemorrhage and he had a theory to account for it. In one prophetic paragraph he discussed the dangers and possible benefits of the transfusion of blood.

Osler² classifies these anemias as follows: (1) Anemia secondary to postpartum hemorrhage; (2) severe anemia of pregnancy; (3) postpartum anemia; (4) acute anemia from puerperal sepsis. However, anemias resulting from hemorrhage or sepsis associated with pregnancy do not differ materially from those due to similar causes not so associated. It seems clearer, therefore, to restrict the definition so as to include only severe anemias beginning during or shortly after pregnancy, not due to obvious complications, but apparently resulting from the gravid state *per se*.

The writer has observed 17 cases that seem to come within this definition, and has classified them on the basis of the blood pictures. Whether the various types differ from one another etiologically cannot, of course, be stated at the present time. It may be that the difference is primarily one of severity, but each case in this series falls so definitely into one group or another, without intermediate forms, as to suggest that the difference is more fundamental.

Case Reports. SEVEN CASES WITH THE BLOOD PICTURE OF SECONDARY ANEMIA. CASE I.—A Yiddish woman, aged twenty-four years, had acute arthritis in 1910, resulting in valvular heart disease. She remained somewhat pale and dyspneic, and these symptoms became severer as pregnancy advanced. Her fifth

baby was born in May, 1915. Delivery was complicated by slight hemorrhage; but there was neither sepsis nor fever. Five weeks later, she was pale, with a yellowish tinge. The heart was moderately enlarged and there was a definite presystolic murmur and a thrill. The liver and spleen were normal. The blood picture was that of a severe secondary anemia (Table I). She recovered from the anemia but died of mitral stenosis, in 1922.

CASE II.—An American woman, aged forty-two years, stated that she had "been yellow all her life," and had been pale for several months. Her eleventh child was born, at term, on March 10, 1923. The easy, low forceps delivery was not associated with any unusual loss of blood. Shortly after delivery she collapsed, and was sent to the hospital. On the fourth day she was "pale, with a buffy-yellow tinge," probably a bit cyanotic. There was no demonstrable enlargement of either liver or spleen. The blood (Table I) showed anemia of the secondary type. Her temperature remained normal. She improved somewhat and left the hospital against advice on the seventh day.

She was readmitted in January, 1925, eight months along in her twelfth pregnancy. She was moderately pale and somewhat puffy. Liver and spleen were normal. The anemia was less in degree but the same in type as before (Table I). Under ordinary hospital care and the administration of iron, she underwent marked improvement. She was delivered at term and soon after left the hospital against advice.

CASE III.—An American woman, aged twenty-eight years, gave a history of dyspnea and edema dating from the termination of her seventh pregnancy in 1921. On July 3, 1923, she was admitted in labor at full term, this being the eighth pregnancy in a period of nine years. Labor was precipitate and there was no hemorrhage. After delivery she collapsed, but recovered and went through her convalescence without fever or obstetrical complications. On the second day she was "pale, with a distinct yellowish tinge, the scleræ bluish." There was a systolic murmur, but no cardiac enlargement. The spleen was easily felt. The liver was normal. The blood (Table I) showed severe anemia of the secondary type. She was transfused on the seventh day, and discharged in excellent condition a month later. The murmur had disappeared, but the spleen was still palpable. In January, 1925, she was still well.

CASE IV.—An Italian woman, aged thirty-eight years, gave a story of malaria in Italy and of a severe hemorrhage following the birth of her fifth baby in 1912. After coming to this country in 1914, she had four normal deliveries and three abortions. One of the latter, in 1922, was accompanied by considerable bleeding. In May,

TABLE I.—ANEMIAS OF SECONDARY TYPE.

Case No.	Date.	Hemoglobin, per cent.	Erythrocytes.								Leukocytes.							Platelets, thousands per c.mm.
			Total, millions per c.mm.	Color index.	Achromia.	Anisocytosis.	Poikilocytosis.	Polychromatophilla.	Basic stippling.	Reticulocytes, per cent.	Normo.	Meg.	Total, thousands per c.mm.	Polynucleophils, per cent.	Eosinophils, per cent.	Neutrophils, per cent.	Large mono. and transitional, per cent.	
I	June 10, 1915	30	2.28	0.65	++	++	++	+	0	..	0	0	6.8	Normal.
II	Mar. 13, 1923	47	3.29	0.71	++	++	++	+	0	9.1	0	0	7.0	81	1	0	0	Decreased.
	Jan. 14, 1925	61	4.33	0.70	++	++	++	+	0	4.5	0	0	12.8	81	0	3	0	264
	Feb. 12, 1925	89	4.50	0.99	0	0	0	0	0	2.4	0	0	Normal.
	July 5, 1923	31	2.34	0.66	++	++	++	++	0	5.6	0	0	11.0	82	0	17	1	156
III	Aug. 9, 1923	50	4.20	0.60	++	++	++	++	+	5.3	0	0	5.0	45	8	35	12	112
	Nov. 3, 1923	82	5.74	0.71	1.4	0	0	11.0	69	3	23	4	240
	July 17, 1923	25	1.70	0.74	+	++	++	+	0	2.2	0	0	5.6	47	2	46	5	Normal.
	Nov. 11, 1924	56	4.04	0.69	++	+	+	0	0	3.0	0	0	7.7	58	1	28	13	Decreased.
IV	Jan. 13, 1925	75	5.00	0.75	6.6	14.0
	Apr. 11, 1924	39	3.38	0.57	++	++	++	0	0	13.6	0	0	9.5	77	1	19	1	390
	May 1, 1924	35	2.90	0.60	++	++	++	0	0	8.2	1	0	40.0	97	0	1	1	178
	May 22, 1924	52	4.80	0.54	++	++	++	0	0	7.0	..	0	10.6	80	5	18	2	372
V	Jan. 21, 1924	40	4.30	0.44	++	++	++	+	0	3.2	0	0	18.6	84	0	12	4	300
	Aug. 7, 1924	50	5.00	0.50	++	++	++	0	0	2.2	0	1	5.4	75	0	21	1	220
	Aug. 22, 1924	60	5.80	0.52	+	17.0
	Jan. 23, 1925	36	3.42	0.53	++	++	++	++	0	..	0	0	11.0	90	0	7	2	Normal.
VI	Jan. 30, 1925	37	3.19	0.58	++	++	++	++	0	..	0	0	8.0	83	3	9	4	Abundant.
	Mar. 6, 1925	48	-3.65	0.66	++	++	++	+	0	5.0	0	0	4.2	Increased.

1923, she gave birth to a healthy baby at term, without undue loss of blood. When seen, a month later, she was pale, with the swarthy tinge of her race. The heart and lungs were normal. Both liver and spleen were easily felt, the edge of the latter being noted as nodular. Although the Wassermann reaction was twice positive, there was no other evidence of syphilis. Pelvic examination was negative. There was no fever. The blood picture was that of a secondary anemia (Table I). The gastric contents after a test breakfast contained no hydrochloric acid; the total acidity was 25. She steadily improved and was discharged well.

CASE V.—An American woman, aged forty-two years, stated that she had been pale since a pelvic operation (appendix, left ovary and uterine fibroid) about 1910. In 1910 she had a nervous breakdown, accompanied by marked increase in pallor. She was admitted in April, 1924, late in her fifth pregnancy, with a history of increasing dyspnea and edema since the seventh month. She was pale, but not yellow, the scleræ slaty. The heart was normal in size and presented an obscure systolic murmur. The liver and spleen were normal. There were a few purpuric spots on the chest. The uterus was the size of an eight and a half months' pregnancy. The urine contained a faint trace of albumin, but no casts. The blood picture was that of a severe secondary anemia (Table I).

Cesarean section was done thirteen days later. The baby weighed seven and a half pounds, and did well. Although there was no excessive loss of blood, she was transfused with 250 cc of blood by the citrate method immediately after operation. Unfortunately the abdominal wound became infected, and convalescence was slow. The hematologic effects of this complication and the subsequent improvement are shown in Table I. She was still in good health in August, 1924.

CASE VI.—A Polish woman, aged thirty-two years, was admitted on June 9, 1924, in premature labor in the eighth month of her sixth pregnancy. She shortly gave birth to twins. There was no undue loss of blood. From the second to the fourth day there was slight fever, and on the sixth day a mild breast abscess appeared. When first seen by the writer, on the twelfth day, she was very pale, without yellowish tinge. There was a systolic murmur at the pulmonic area. The spleen was palpable, the liver normal. The blood (Table I) showed anemia of the secondary type. She improved slowly and was discharged at the end of six weeks. She was readmitted a fortnight later with acute polyarthritis, from which recovery was prompt. The systolic murmur persisted. The spleen was not palpable at this time. Her present condition is unknown. Both the premature babies died within a few weeks.

It is perhaps doubtful whether this case should be included in the

series, as the anemia was not carefully studied until after the onset of the breast abscess. Pallor, however, preceded the infection and the latter did not seem virulent enough to account for the degree of anemia that was present so early.

CASE VII.—An Irish woman, aged thirty-one years, was admitted on January 22, 1925, in labor at term, this being her first pregnancy and an illegitimate one. Pregnancy was normal, except for edema in the last two weeks. Delivery was spontaneous and there was no undue loss of blood. When seen, next day, she was moderately pale, the face somewhat puffy. Systolic blood pressure 160; diastolic 80. There was a slight systolic murmur, without cardiac enlargement. Spleen and liver normal. Urine normal. The blood was that of a severe secondary anemia (Table I). She was kept under observation for nearly two months. Although her general condition improved markedly, the blood figures rose so slowly that transfusion was advised. It was refused by the patient. The baby did well.

Comment. These 7 cases are classed together primarily because all showed the secondary blood picture, but the clinical resemblance is equally striking. All were afebrile except 2, and these had no fever until the onset of late septic complications. They were not very sick. The grade of anemia was severe enough, the average lowest hemoglobin being 35 per cent, but the anemia was not progressive, all began to improve at once after delivery or as soon as treatment was begun. Four were not transfused and, of the others, 2 were transfused only to expedite convalescence and 1 to make safer the necessary operative delivery. So far as is known none of them relapsed. Obviously the outlook is good.

A consideration of the individual histories in this group will show that nearly all the women were below par before the last pregnancy began, some of them giving clear stories of previous attacks of anemia, hemorrhage in preceding pregnancies or definite infections of severe type. This fact has also been noted by Adler.¹⁹ Moreover, with the exception of Cases I and VII all had had numerous and frequently repeated pregnancies, the average number being 7.1.

Taking the patients' statements for what they are worth, symptoms began during pregnancy in 4 cases, and immediately after delivery in 2.

These cases are possibly related to the mild chloro-anemia which is seen so frequently in midpregnancy^{10, 15} and in the puerperium⁴ as to be classed as quasi-physiological by some authors. They are probably quite common, but the milder ones are not often referred to the internist for study.

EIGHT CASES WITH THE PERNICIOUS BLOOD PICTURE. CASE VIII.—An American woman, aged twenty-six years, gave a history of a

TABLE II. — ANEMIAS OF PERNICIOUS (VIII-XV) AND APLASTIC (XVI) TYPES.

Case No.	Date.	Hemoglobin, per cent.	Erythrocytes.								Leukocytes.						Platelets, thousands per c.mm.					
			Total, millions per c.mm.	Color index.	Volume index.	Achromia.	Anisocytosis.	Poikilocytosis.	Polychromatophilia.	Basic stippling.	Reticulocytes, per cent.	Nucleated cells per 100 w.b.c.		Total, thousands per c.mm.	Polynucleotrophils, per cent.	Eosinophils, per cent.		Mast cells, per cent.	Lymphocytes, per cent.	Large mono. and transitional, per cent.	Myelocytes, per cent.	
												Normo.	Abn.									
VIII	Feb. 20, 1906	31	1.12	1.41	+	0	++	+	++	+	0	..	1	5	3.3	64	1.0	0	33	2.0	0	Normal.
IX	Apr. 7, 1906	10	0.73	0.67	..	0	++	+	++	+	+	..	1	2	10.2	63	1.5	0.5	29	5.0	1	Normal.
X	June 5, 1907	30	1.20	1.25	++	..	+	..	++	0	4.2	78	0.5	0.5	18	3.0	0	Normal.
	June 9, 1907	12	0.43	1.33	..	0	++	+	++	+	++	0	5.4	78	0.5	0.5	18	3.0	0	
XI	Jan. 27, 1913	20	0.67	1.54	1.80	0	++	+	++	+	++	..	3	20	7.0	69	0	0	26	2.0	3	Normal.
	Dec. 10, 1914	93	5.20	0.89	..	0	0	+	0	0	0	..	0	0	9.7	59	0	2.0	39	0	0	
XII	Nov. 8, 1919	12	0.59	1.00	-	0	++	+	+	0	0	4.0	0	2	3.1	34	0	0	62	4.0	0	106 500
	Jan. 14, 1924	98	3.70	1.43	..	0	0	0	0	0	0	0.8	0	0	4.4	63	3.0	0	28	5.0	0	
	Nov. 10, 1924	84	4.36	0.97	..	0	0	0	0	0	0	0.4	0	0	4.8	64	5.0	0	26	3.0	0	
XIII	May 22, 1922	29	1.42	0.97	n.	0	+	+	+	+	0	..	0	5	2.0	73	0	0	22	5.0	0	136
	June 6, 1922	54	2.44	1.10	1.12	+	++	+	0	0	0	..	1	1	5.9	84	1.0	0	10	3.0	2	288
	July 10, 1922	80	3.76	1.07	1.06	0	+	+	0	0	0	..	0	0	6.1	75	3.0	0.5	14	7.5	0	336
XIV	Aug. 29, 1924	19	0.66	1.46	1.33	0	++	+	++	+	+	11.0	8	16	6.4	64	1.0	0	27	2.0	6	56
	Sept. 30, 1924	90	4.42	1.02	..	0	+	0	0	0	0	-0.4	0	0	4.8	45	5.0	4.0	40	6.0	0	88
XV	Feb. 3, 1925	28	1.08	1.27	..	0	++	+	+	+	+	2.5	0	0	2.5	58	0	0	40	2.0	0	200
	5, 1925	49	1.60	1.53	3.0	2.6	120
	11, 1925	48	1.72	1.41	2.8	51	2.0	1.0	41	5.0	0	
XVI	Mar. 5, 1925	96	4.10	1.17	..	0	0	0	0	0	0	0.6	0	0	1.8	51	2.0	1.0	41	5.0	0	120
	Nov. 1, 1922	20	0.78	1.25	-	0	+	+	+	+	0	0.4	0	0	2.6	48	1.0	0	49	2.0	0	64

seven months' miscarriage two years before I saw her. During this previous pregnancy she suffered from diarrhea and a sore mouth, which frequently bled, these symptoms persisting until two months before my examination. She was pale, but not at all yellow. The tongue was smooth, with red patches about its edge. There was a systolic murmur. Neither liver nor spleen was palpable. The blood picture (Table II) was typically pernicious. She was soon after delivered of a dead fetus and in a few weeks died of anemia.

CASE IX.—An Irish woman, aged twenty-two years, was seen when seven months along in her first, an illegitimate, pregnancy, early in which symptoms of debility began. The day before I saw her there was a chill and fetal motion had ceased. The color was "a transparent yellow, with marked cyanosis." There was a systolic murmur. The spleen was 2 inches below the costal border. She was "almost moribund." The blood (Table II) showed extreme anemia. The color index was so low as to suggest that this case should be classed among those with the secondary picture. But the hemoglobin was estimated by the Tallqvist method, which is not accurate for these low percentages. The leukocytosis is accounted for by the death of the fetus. In other essential respects, especially in the absence of achromia and the predominance of megaloblasts, the picture is clearly pernicious. A recent examination of the smear, now eighteen years old and badly faded, gives no reason to change this opinion. A few days after I saw her she was delivered of a dead fetus. She improved a bit and then died, apparently from anemia.

CASE X.—An Irish woman, aged thirty-four years, was delivered in February, 1907, without undue loss of blood. Vomiting, which had been somewhat excessive during pregnancy, persisted after confinement. In May she raised a small amount of blood. She was admitted on June 4, 1907. Although vomiting persisted, there was no hematemesis, and the guaiac test showed no blood either in the vomitus or stools. She was "pale, with slaty conjunctivæ." The liver was two fingers below the costal margin; the spleen was normal. The blood (Table II) showed a fairly typical picture of pernicious anemia. She died July 16, five months after her confinement.

CASE XI.—An American woman, aged twenty-eight years, was seen in consultation on January 27, 1913. Her mother was said to have died of "consumption of the blood." Her three pregnancies had been normal. Early in the last one she had erysipelas. She was delivered of a healthy full-term baby three months before I saw her. After her confinement debility and pallor continued to increase slowly. The temperature varied from normal to 100°. There was

no particular loss of blood at confinement, but from time to time afterward she passed small amounts of bright blood by rectum. She was "very pale, yellowish with a slightly waxy look." The heart area was normal, but there was a loud systolic murmur. The blood presented a typical pernicious picture (Table II). She soon began to improve and recovered completely. She has gone safely through two more pregnancies (1917 and 1919). The first one was followed by "slight anemia," the second was without incident. She is now (December, 1924) in excellent health.

CASE XII.—A woman, aged thirty-two years, presented a history of syphilis beginning about 1910, and from May, 1918, nearly up to the time of admission she was treated continuously at the Boston Dispensary with diarsenol, arsphenamin and salicylate of mercury. While under our care there was no evidence of this disease and the Wassermann reaction was negative. Her fifth pregnancy terminated, normally and at full term, on March 28, 1919, without undue loss of blood. Following confinement she suffered from an unusual and increasing sense of weakness. In August she became quite pale. Early in September she had tonsillitis followed by a crop of purpuric spots on the legs and arms, on account of which she was sent to us. She presented an extreme yellowish pallor. The spleen was palpable. There was a systolic murmur, without enlargement of the heart area. Otherwise physical examination was negative. The blood (Table II) showed anemia of extreme degree and with the pernicious picture.

Owing to a delay in obtaining a donor she was not transfused until October 12, by which time she was desperately ill. She then received 650 cc of blood, by the Kimpton-Brown method. After transfusion there was marked edema of the lungs and some fever. She remained unconscious or delirious for several days and then began to improve. Since her recovery she has gone through her sixth pregnancy without recurrence of the anemia. Today she is perfectly well, though the color index remains high.

CASE XIII.—An American woman, aged twenty-six years, was delivered of her second baby on May 4, 1923. Pregnancy had been uncomplicated except that in the later months there had been considerable pain in the right abdomen, and increasing pallor after the sixth month. She "went over her time" and labor was finally induced. Delivery was by low forceps. There was not much hemorrhage. The baby weighed 8 pounds and did well. On the day after confinement the temperature began to rise, reaching 102° at the end of a week. Although there was no evidence of sepsis except the fever, she was gently curetted. Fever persisted and pallor increased. The temperature chart is herewith depicted.

There was "marked straight pallor," and considerable pigmentation

tion. The heart was rather large and there was a slight systolic and a doubtful diastolic murmur. The liver was normal. The edge of the spleen was about 2 cm. below the costal margin. The blood picture was pernicious in type (Table II).

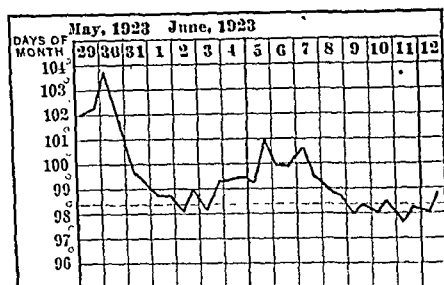
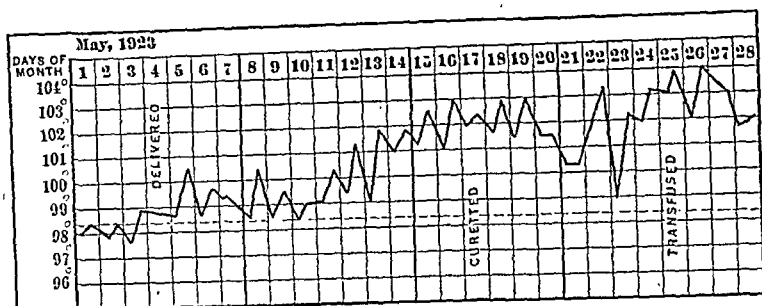


CHART I.—Case XIII. Temperature chart.

She was transfused (600 cc) by Dr. A. R. Kimpton, by the paraffined tube method, on May 26. Although the hemoglobin showed a rise of 19 per cent later in the day, there was little immediate clinical improvement. On the 29th she still had a temperature 103° and a pulse of 156, the mind was clouded and she looked badly. She became delirious and a few rales appeared in her right lower lobe posteriorly. By May 31, however, her temperature had fallen to normal and convalescence thereafter was rapid. The spleen was not felt after June 13. There has been no relapse.

CASE XIV.—An American woman, aged thirty-two years, gave birth to her first baby at term on July 23, 1924, without unusual loss of blood. Late in pregnancy she had several slight nosebleeds, but was not anemic. She continued to flow up to August 29. The temperature remained between 99° and 100° F. She was extraordinarily pale, with a slightly yellowish "sour-dough" tinge. There was no hemorrhage from the mucous membranes and none in the skin except a few pin-point spots on the upper front chest. The blood (Table II) presented a perfectly typical pernicious picture.

Within the next four weeks she was transfused four times by Dr. Kimpton, a total of about 2000 cc being given. On September 30, 1924, she was practically well, the color being about normal,

the spleen no longer palpable and the blood nearly up to the normal standard. She has remained perfectly well ever since, and the baby is normal.

CASE XV.—An American woman, aged twenty-seven years, had her second baby on November 30, 1924, after a pregnancy which was normal except for rather severe vomiting in the early months, and attacks of pain and tingling in the arms during the last two. There was no especial loss of blood at parturition, but three days later she had a sore mouth. In mid December she began to suffer from weakness, pallor, headache and dyspnea, which increased in severity up to admission, on February 2, 1925. During the six weeks she lost about 20 pounds. On admission she was very pale, with a muddy yellow tinge not at all striking. The heart was normal; the edge of the spleen was 4 cm. below the costal margin; the liver was just palpable. The blood (Table II) showed the pernicious picture.

On the day of admission the temperature was 103°. On February 4 she was transfused, 500 cc, by Dr. Kimpton. There was marked immediate improvement in the general condition and in the blood, and the fever began to subside. Although the improvement was maintained, it was not progressive and she continued to show an afternoon temperature of about 100°. On February 13 transfusion was repeated and thereafter improvement was rapid up to discharge on March 5.

Comment. In drawing a contrast between these cases with the pernicious picture and the previously described group, it is at once evident that we are dealing with a much more severe condition. Four occurred in pretransfusion days, and three of them died. All 4 of the more recent cases were transfused, and all recovered. My impression is that without transfusion the mortality in the whole group would have been 6 or 7 instead of 3.

At least 5 of these patients had more or less fever, and in some it was marked. The liver was palpable in 2 cases, the spleen in 5. The influence of repeated pregnancies was less marked than in the patients showing the secondary type of anemia, the average being 2.3 as contrasted with 7.1. Two cases delivered themselves prematurely, the fetus in each being dead. Six went to term, the 5 babies whose fate is known doing perfectly well.

As in the secondary group, it is difficult to date the onset of the anemia. In 3 it surely began before confinement, and probably rather early in pregnancy. In the other 5 it *seems* to have started only after parturition, at least neither patient nor their physicians suspected anemia earlier. Indeed in 2 instances it developed so slowly that the serious nature of the gradually increasing debility and pallor was not obvious for several months, and when the condition did become severe its causal association with pregnancy was lost sight of. The writer must confess that in Cases XI and XII

his own diagnosis at the time was pernicious anemia, and that the true nature of the disease did not strike him until months and years passed without the expected relapse. This slow, gradual onset after normal pregnancy and normal parturition was not seen in any of the cases showing the secondary blood picture.

A CASE WITH THE APLASTIC BLOOD PICTURE. CASE XVI.—An Irish woman, aged thirty years, was seen when three months along in her second pregnancy. For a month she had been complaining of debility, "fainting spells," and slight dyspnea, and there had been considerable morning vomiting. She was very pale, but not yellow; the scleræ slaty. The heart presented a loud systolic murmur and a suggestion of a presystolic. The liver edge could just be felt on deep inspiration; the spleen could not be palpated. There were two small ecchymotic areas on the right shin, which she could not account for. The blood showed a fairly definite aplastic type of anemia (Table II).

She was given two transfusions with little or no effect. As she had slight convulsions, possibly hysterical, at each attempt, only 250 cc of blood could be given. No effort was made to terminate the pregnancy. She died about three weeks later.

Comment. This case is classed as aplastic because of the great reduction of platelets and the absence of evidence of regeneration of the red corpuscles. The neutrophilic leukocytes are rather higher than is usual in outspoken aplasia, the absolute number being 1248 per c.mm. For this reason perhaps it is better called hypoplastic than aplastic. This picture is rarely seen in the anemias of pregnancy, but it is not unique, a somewhat similar instance having been reported by Jungmann.⁶ In his case the aplasia was less striking than in mine, since erythroblasts were present, the neutrophiles were 7592 (73 per cent of a total leukocyte count of 10,400), and there were a few myelocytes. Jungmann's patient, who was seen at the end of pregnancy, was safely delivered, and afterward recovered.

AN ATYPICAL CASE WITH RECOVERY AFTER SPLENECTOMY. CASE XVII.—An American woman, aged thirty-one years, had endocarditis and pericarditis, with pallor and edema in 1918, during her second pregnancy. In August, 1923, during the seventh month of her third pregnancy these symptoms recurred. As the urine contained albumin and casts, her physician attributed the symptoms to nephritis. She was delivered, at eight months, on September 17, 1923. Very little blood was lost, and the baby did well.

On October 1, she was "extremely pale and transparent, but not yellow." There was a loud systolic murmur. The liver was slightly enlarged. The spleen was greatly enlarged, its lower border being

below the level of the umbilicus. On the legs were a few small ecchymoses, which she was unable to explain. Pelvic examination showed nothing remarkable. The temperature was 101° F. (see chart). The blood pressure was normal. The urine, on entrance, contained a minute trace of albumin and a few casts; several subsequent analyses were normal. The blood picture (Table III) will be discussed later.

During the next six weeks seven transfusions, totaling 3700 cc of blood, were given. By these vigorous measures it was possible to get the hemoglobin and red corpuscles up to fairly high figures. The temperature which was at first high and irregular, fell nearly to normal, and general improvement was manifest. On the other hand, as a glance at Table III will show, the anemia immediately

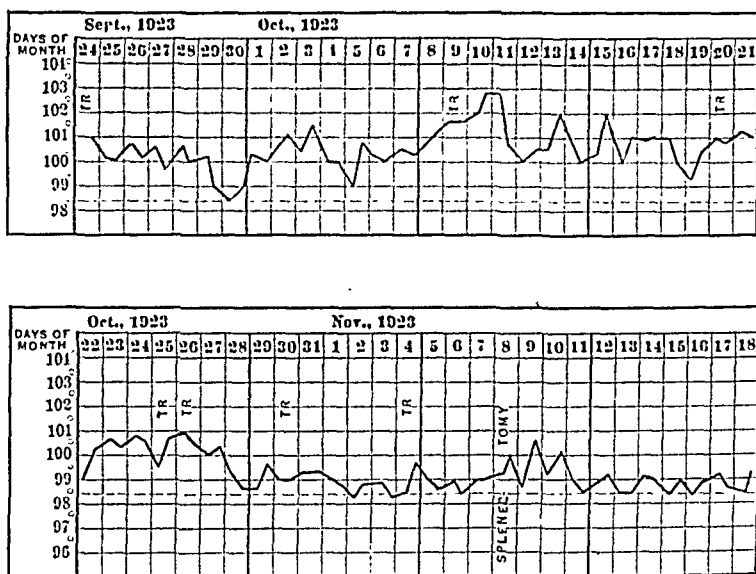


CHART II.—Case XVII. Temperature chart. (Tr. indicates dates of transfusions.)

and rapidly increased as soon as transfusions were stopped. This was not the result of hemorrhage, as the only loss consisted of very slight uterine oozing. There was no material change in the spleen.

Splenectomy was decided upon in view of the facts: (1) That hemolysis was very active, her serum being intensely yellow; (2) that the spleen was enormously enlarged, and (3) that there was marked fragility of the red corpuscles; hemolysis in hypotonic solutions of sodium chloride began at 0.575 per cent and was complete at 0.400 per cent (the normal figures are 0.425 and 0.325 per cent). The operation was performed by Dr. A. R. Kimpton on November 8. Without further transfusion the blood at once began to improve and within a week recovery seemed certain: Convalescence was, however, interrupted by phlebitis of both legs, lasting

TABLE III.—CASE XVII. ATYPICAL ANEMIA.

Case No.	Date.	Hemoglobin, per cent.	Erythrocytes.										Leukocytes.							Platelets, thousands per c.mm.
			Color index.	Achromia.	Anisocytosis.	Poikilocytosis.	Polychromatophilia.	Basic stippling.	Reticulocytes, per cent.	Normo.	Nucleated ce's per 100 w.b.c.	Total, thousands per c.mm.	Polyneutrophils, per cent.	Eosinophils, per cent.	Mast cells, per cent.	Lymphocytes, per cent.	Large mono. and transitionals, per cent.	Myelocytes, per cent.		
XVII	Sept. 24, 1923	16	1.07	0	++	+	++	++	Transfused, 4.0	10	21	14.0	62	0	0	22	0	14	56	
	24, 1923	24	1.04	+	++	++	++	++	Transfused, 8.8	3	9	10.8	73	1	1	11	1	13	56	
	Oct. 3, 1923	17	0.63	Transfused, 5.2	500 cc.	.	1.8	Decreased.	
	9, 1923	15	0.94	0	++	+	+	+	Transfused, .	500 cc.	.	3.4	82	
	20, 1923	52	1.00	Transfused, 4.8	500 cc.	.	4.8	104	
	24, 1923	66	1.10	0	++	+	+	++	Transfused, 4.6	1	4	2.8	62	4	1	24	6	3	72	
	25, 1923	47	1.00	Transfused, 3.4	500 cc.	.	5.0	92	
	26, 1923	38	1.06	Transfused, 4.4	600 cc.	.	12.8	89	1	0	8	2	0	272	
	29, 1923	51	0.88	0	++	+	++	++	Splenectomy. 4.4	95	11	11.2	70	4	0	19	3	4	284	
	30, 1923	44	0.64	+	++	++	++	++	Transfused, 3.8	97	3	13.0	64	7	1	19	0	9	404	
	Nov. 1, 1923	55	0.87	Transfused, 1.6	44	3	14.0	88	0	0	7	5	0	256	
	3, 1923	2.60	0.96	+	++	++	++	+	Transfused, 8.8	39	0	28.0	85	1	0	7	5	2	256	
	4, 1923	4.20	0.75	+	++	++	++	0	Transfused, 7.2	15	0	16.0	46	7	1	36	9	0	652	
	8, 1923	63	0.75	+	++	++	++	0	Transfused, 7.0	4	0	8.6	67	3	1	22	2	5	350	
	8, 1923	104	1.25	0	++	++	++	0	Transfused, 3.5	0	0	10.0	53	2	2	43	0	0		
	9, 1923	104	1.33	+	++	++	++	+		0	0									
	12, 1923	104	0.99	+	++	++	++	+		0	0									
	16, 1923	100																		
	28, 1923	100																		
	Dec. 7, 1923	104	1.25	0	++	++	++	0												
	Jan. 24, 1923	104	1.33	+	++	++	++	+												
Apr. 1, 1923	104	1.33	+	++	++	++	+													
Sept. 10, 1923	100	0.99	+	++	++	++	+													

through December. On January 30, 1924, she was discharged well. In August, 1924, she had a mild attack of acute polyarthrititis. She is now (March, 1925) perfectly well.

Dr. F. B. Mallory examined the spleen and reported as follows: "The spleen measures 22 x 12 x 9 cm. It is dark reddish-brown in color and firm in consistency. The cut surface is dark crimson and yields a moderate amount of pulp on scraping. Microscopically it shows congestion. The blood sinuses contain many undifferentiated cells, which are often grouped in small and large clumps. Each cell is surrounded by a moderate amount of basophilic cytoplasm. Mitoses occur in moderate numbers. All stages of differentiation between these cells and neutrophilic and eosinophilic leukocytes can be traced. Eosinophiles are very numerous and are located mostly in the pulp and often in clumps. No megacaryocytes or erythroblasts can be found. Diagnosis: Hypertrophy of spleen due to myeloblastic function."

This case is apparently unique. The blood picture, particularly the first two examinations recorded in the table, is difficult to classify. The numerous nucleated red corpuscles, with megaloblasts predominating, and the rather high color index suggest pernicious anemia. But the neutrophile leukocytosis is not thus explainable and the presence of numerous myelocytes in a patient with an enormous spleen brought up the question of leukemia. Hemolysis of fragile red corpuscles was obviously present. I believe that hemolysis was abnormally active and the presence of myelocytes is doubtless, in part at least, explained by the myeloblastic hyperplasia within the spleen. The apparent aplasia of the platelet-producing elements of the marrow, and later also of those producing leukocytes, was probably of the same nature as that seen in pernicious anemia—perhaps due to replacement of these cells by the intense hyperplasia of those producing red corpuscles.

The changes in the blood following splenectomy do not differ from those observed by many writers^{13, 16} and they need not be discussed here.

General Comment. The *etiology* of these anemias is obscure. Some attribute them to the damage wrought on the hemopoietic organs by hemorrhage and infection. Some consider them an intensification of the "physiological chloro-anemia" of pregnancy.

Adler¹⁹ believes that all the anemias of pregnancy occur in women who are predisposed, or who are already suffering from some other form of anemia, especially chlorosis, posthemorrhagic or secondary anemia, but rarely, if ever, from ordinary pernicious anemia. In such women, the added strain of pregnancy upon the blood-forming organs, results in pathologic conditions of greater or less severity and of varying types.

A more elaborate theory is that of Hoffbauer. As quoted by

Rowland,⁹ this is to the effect that a syncytial hemolysin is produced in the ectodermal cells of the chorion. Later an antihemolysin is formed in the maternal blood, which accounts for the disappearance of the slight anemia so frequently observed in the early months of normal pregnancy.¹⁰ If such antibodies fail, a destructive anemia persists.

Carrel and Ebeling,¹² in a study of the growth of fibroblasts in the serum of old animals as compared with that of young ones, found evidence that the serum in adults contains some factor that inhibits cell growth. Galloupe and O'Hara,¹¹ basing their views upon this work, suggest that parturition may deprive the blood-forming tissues of some influence which they have been receiving from the fetus, and that a progressive anemia might result when the hemopoietic mechanism fails to compensate.

Finally, McQuarrie¹⁷ has studied the isoagglutinins in the blood of newborn babies, with reference to the occurrence of toxemia of pregnancy in the mothers. Among the relatively small proportion of babies who have such isoagglutinins at birth, toxemia is 16.5 times as common where the maternal and fetal bloods are incompatible as when they are in the same group. It is possible that the hemolytic anemia of pregnancy, which has many points of resemblance to toxemia, may be connected with the same causes.

However suggestive these theories may be, they must be regarded for the present rather as leads for further study than as lucid and satisfactory explanations of the clinical facts.

Diagnosis and Relation to other Diseases. There are considerations both historical and hematological which invite a discussion of the relations between ordinary pernicious anemia and anemias of the pernicious type associated with pregnancy. But there are difficulties in the way of discussing with profit the fundamental relationship that may exist between two diseases in neither of which the etiology is known! In ordinary pernicious anemia everything points to a primary process of excessive hemolysis with a secondary hyperplasia of the marrow, compensatory in nature but abnormal in output. In the cases under discussion there is reason to suppose that the anemia is likewise hemolytic in origin and that the intense hyperplasia of the marrow is similar in nature. Further than this, existing evidence will not take us.

There is much confusion amongst writers on this subject, as regards both terminology and point of view. To many the similarity in blood pictures seems to justify the assumption that the "pernicious anemia of pregnancy" is identical with ordinary pernicious anemia. Adler,¹⁹ however, clearly distinguishes between true pernicious anemia and "anemia graviditatis pernicioformis." He considers that they have nothing to do with one another, and that true pernicious anemia is very rarely seen in pregnant women.

From the clinician's standpoint the two diseases are as far apart

as the poles. In one the anemia is invariably fatal in the end, regardless of treatment. In the other nearly all cases will, with proper treatment, recover permanently. If the physician responsible for the lives of his patients will bear this one fact in mind, he need not lie awake nights worrying as to whether the two diseases are fundamentally distinct or merely the result of minor variations of the same underlying process.

Does ordinary pernicious anemia ever occur in pregnant or parturient women? The question could be answered in the affirmative by the demonstration of: (1) Cases in which a diagnosis of pernicious anemia in a nullipara has been established beyond reasonable doubt, and where pregnancy subsequently ensues, or (2) cases where anemia of the pernicious type is recognized during pregnancy and afterward runs a relapsing and remitting course with ultimate fatal termination and the postmortem lesions of pernicious anemia. I have never seen a case of either sort. Heim,¹⁴ who recognizes the occurrence of pernicious anemia in pregnancy as a rare coincidence, reports one case in which conception apparently occurred during a remission, but exact data as to the condition of the blood previous to pregnancy are lacking. Indeed, in a doubtless incomplete survey of the literature, I have encountered not a single instance which can be accepted without reservation. This is rather remarkable, since ordinary pernicious anemia, although it occurs most frequently in women, as in men, during the fifth decade, is by no means rare in women of child-bearing age.

Anemia from ordinary obstetrical hemorrhages will seldom be confused with the type under discussion. The writer has seen blood pictures approaching the pernicious type as a result of successive severe hemorrhages, but ordinarily the picture, as soon as regeneration is fairly established, is clearly of the secondary type. A woman, after a postpartum hemorrhage, normally begins to improve rapidly within a few days. It is only where the anemia continues to progress, or where it is all out of proportion to the amount of blood lost, that doubt can arise. As hematologists occasionally see cases of obvious posthemorrhagic anemia not due to pregnancy, which are followed by such unusual results, their relationship to the conditions under discussion is questionable.

As many patients with anemia of pregnancy have heart murmurs and some have irregular fever, it is only natural that they should occasionally be mistaken for malignant or septic endocarditis. Particularly in the subacute bacterial form of endocarditis there may be notable enlargement of the spleen and severe anemia. The latter is almost always of the secondary type, with leukocytosis, as in other infections.⁷ The association with pregnancy, the invariably negative blood cultures, the absence of embolic phenomena and the prompt recovery after transfusion with the disappearance

of fever, and usually of the murmurs, will make the differentiation clear.

It would seem almost inevitable that cases of postpartum anemia of the pernicious type should occasionally be mistaken for puerperal sepsis to the quite undeserved chagrin and humiliation of the obstetrician. The temperature may closely simulate that of sepsis and some degree of leukocytosis is not infrequently present, while the pallor of the patient is by no means incompatible with such a diagnosis. The obstetrician confronted with a case of apparent sepsis, in which pallor is a marked feature, will do well to make a thorough study of the blood. If the anemia is of the secondary type, with polymorphonuclear leukocytosis, it will point strongly toward sepsis. But if the picture is that of pernicious anemia, and particularly if there is also leukopenia, immediate transfusion should be done. If there is a prompt drop of temperature and progressive improvement after a single transfusion, infection as a cause is most improbable. In real septic infections transfusion has no such influence—albeit the operation is not infrequently performed with just this object in view.

Of course the future may show that perperal anemia is due to infection with some organism at present unknown, or that the disease is due to some influence not at present clear, of infection with known pyogenic cocci upon the hemopoietic mechanism. But at present such a hypothesis is pure speculation. And let me add that one's "index of skepticism" must indeed be low if he can believe that these terrible, acute anemias are the result of chronic foci of infection in teeth or tonsils, and can bring himself to hope for relief from their eradication.

Finally, the occurrence of similar types of anemia, of like severity, early in pregnancy, would seem sufficient proof of the existence of the condition entirely apart from septicemia in the ordinary sense of the word.

The *prognosis* is discouraging only if one has reference to the older literature. Experience seems to show that most of the cases with anemia of the secondary type will get well anyhow. With transfusion and other modern methods available, most of those with anemia of the more severe types will also recover, and may even go through subsequent pregnancies without recurrence. If the disease becomes severe early in pregnancy, the patient will probably abort. The babies, if born at term, generally do perfectly well, and the writer does not at all agree with Esch,¹⁸ who believes that their outlook is poor.

Treatment. The milder cases, showing the secondary blood picture, will usually require only ordinary nursing care, with the use of iron and arsenic, "in which," Osler said in 1919, "I still have faith." As the writer's professional memory dates back to a period when

chlorosis was still an actuality, he has no lack of faith in the older pharmacopeial forms of mineral iron, seldom uses iron hypodermically and does not attempt an increased ingestion of food iron. If mineral iron was absorbed from the alimentary tract in 1900, it is similarly absorbed in 1925. If the same striking effects are not seen today, it is not because the iron or the gut is changed, but because the disease is changed, we are not seeing forms of anemia in which iron therapy is so effective.

Transfusion has made an enormous difference in the outlook for these patients. Even the cases with the secondary blood picture may need it. When the pernicious picture is recognized they should have it without delay. The condition here is different from that in ordinary pernicious anemia. In the latter we know that transfusions will at best only defer the fatal termination. More will probably be called for later, and if one believes that their possible number is for any reason limited, one uses them economically. On the other hand, anemia of the pernicious type associated with pregnancy generally ends fatally without remission if left to itself, while most cases get well permanently if they are transfused. This being so, why wait?

Probably a single transfusion will suffice in the majority of cases, and recovery is sometimes marvelously prompt. Obviously something more has been accomplished than merely supplying more red corpuscles upon which the destructive factor may continue to work. The destructive factor is itself thrown out of gear, or the normal relationship between production and destruction is reestablished. If one transfusion does not do it, the operation should be repeated until it *does*. Seldom will one find himself in the unpleasant situation so common in ordinary pernicious and aplastic anemia of having to decide when to withhold his hand and let the inevitable happen.

The writer prefers the Kimpton-Brown method,⁵ in which paraffined tubes are used without citrate or other anticoagulant, particularly where platelets are low and there is a tendency to hemorrhage. It is a ticklish procedure, however, and requires skill and experience. If these are not available, the citrate method should be used. In the absence of evidence that small amounts are equally valuable, at least 500 cc should be given.

Splenectomy, although it was attended with most brilliant results in one of my cases, is not advocated as a routine procedure. It was undertaken here only because repeated transfusion had failed, and certain recognized indications were present.

In cases originating early in pregnancy the question of emptying the uterus arises. In mild cases of the secondary type it is surely justifiable to let pregnancy proceed. Probably Rowland is in general correct in saying that "any case bad enough to require trans-

fusion is bad enough for termination of pregnancy." This question has caused some discussion amongst writers on the subject.¹⁸ It should be said that the unfavorable results were recorded mostly by earlier writers, who did not have at their command the free use of transfusion. The proper course must depend upon the merits of the individual case, having reference to the type and severity of the anemia, the stage of pregnancy and the viability of the fetus.

Finally there is the question regarding future pregnancies. In one of the cases reported by Galloupe and O'Hara¹¹ anemia recurred with increasing severity in several successive pregnancies, and these writers refer to similar cases in the literature. On the other hand my Case XII has been through a subsequent pregnancy without recurrence and Case XI has been through two. A similar instance is mentioned by Osler. One's personal equation will enter largely into the question. It is fair, however, to bear in mind the hopeful prognosis of the condition today, as compared with the past.

Summary. 1. Seventeen cases are recorded of anemia occurring in pregnancy and the puerperium, all of severe grade. The blood picture may be that of secondary anemia, pernicious anemia, or aplastic anemia, or it may be atypical.

2. All 7 cases with the secondary blood picture recovered. Transfusion seems a question of expediency rather than of necessity.

3. Eight cases presented the pernicious blood picture. Of 4 not transfused 3 died. Four recovered after transfusion.

4. One case of the aplastic type died in spite of transfusion.

5. A highly atypical case recovered, after splenectomy, repeated transfusions having been unsuccessful.

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NONFATAL CARBON MONOXID POISONING.

REPORT OF A CASE.

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PRACTICALLY all the cases of carbon monoxid poisoning hitherto reported have died very shortly after exposure to the gas, and have been so severely intoxicated as to produce serious and profound lesions in the brain. It is of interest, therefore, to report a case of proven carbon monoxid poisoning in which exposure was not sufficient to cause death, but in which the symptoms corresponded to the anatomical distribution of the lesions found in more severe cases. By means of this case also a closer correlation of clinical and pathological findings is possible, for a careful study of the former in a case which has not been killed by the gas, will reveal where and to what extent certain brain areas are affected in the less severe cases, and whether these cases show a progressive degeneration in the areas affected. Aside from this, the progress of a case which has been sufficiently injured by carbon monoxid to produce definite symptoms of brain destruction without causing death is in itself a matter of interest, particularly since very few such cases have been put on record.

Report of Case. HISTORY. Mr. H. Y., a young man aged nineteen years entered the Philadelphia Orthopedic Hospital on November 14, 1924, complaining of numbness in his left face and difficulty with his speech for two weeks. The family history was entirely negative. The patient worked as an installer of furnaces. He was entirely well until three weeks before entrance, or until October 20, 1924. At this time he was engaged in cleaning the boilers in a large plant, while the fire was still going. He inhaled a good deal of coal gas in the procedure, and was at work for forty-five minutes. One hour after the job was completed he complained of numbness of his right leg and of uncontrollable hiccoughs. The hiccoughs persisted, despite attempts to stop them, for seven or eight hours. About five hours after the exposure his right arm felt as if it were asleep. His right leg was still numb. On awakening the next morning his entire right side felt numb, including the right side of his head. He was never unconscious, but he had headache and dizziness from the onset of his illness. The headache had disappeared two days after the onset of his trouble, but his dizziness persisted for some time. The numbness in his right side persisted without abatement for one week, but then gradually grew less,

until at the time of entrance into the hospital it was but slightly apparent. From the beginning he had weakness in his right arm, such as to cause him to drop things readily. About one week before entrance he found that he could not open his right eye very widely and that his speech seemed thick. He could not articulate his words well, and twisted them up.

EXAMINATION. At the time of entrance he was dull and almost stupid. The general physical examination was entirely negative. The heart and lungs were normal. Blood-pressure: 128 systolic, 80 diastolic. The cranial nerve examination was entirely negative. The pupils were dilated but reacted well to light and in convergence. The fundi showed definite congestion of the retinal vessels, but no papilledema. All the other cranial nerves reacted normally. In the motor system one found a definite weakness of the right upper extremity, and a slighter degree of weakness of the right lower extremity. The dynamometer readings gave values of 40 kg. with the right hand and of 70 kg. with the left hand. A moderately coarse tremor of the right hand was elicited, and definite but not severe incoördination with the usual tests. There was also definite incoördination of the right lower extremity. In the Romberg position a definite unsteadiness was apparent. The gait was ataxic with dragging of the right foot, the right leg swinging out in walking and the right foot dropping. The speech was slurring with the usual test phrases. The reflexes of the upper extremities showed more active reflexes on the right side. The patellar and Achilles reflexes were hyperactive on both sides. No pathological reflexes were elicited: no Babinski, Oppenheim or clonus. There was a definite dysphagia, but no loss of swallowing.

LABORATORY EXAMINATION. Examination of the blood revealed: Red cells, 5,230,000; white cells, 9000; hemoglobin, 85 per cent, and a normal differential count. The blood Wassermann was negative. Blood sugar was 111.1 mg. per 100 cc. Blood-urea nitrogen was 13.3 mg. per 100 cc, and the nonprotein nitrogen was 22.6 mg. per 100 cc. Two spectroscopic examinations showed no carbon monoxid spectrum. A chemical examination of the blood revealed a trace of carbon monoxid. One month later, on discharge, this was not present.

COURSE OF ILLNESS. The patient was in the hospital from November 14, 1924, to December 16, 1924, a period of about one month. During his stay in the hospital the striking feature of the case was the great fluctuation in the symptoms and signs which the patient showed. After the third day in the hospital the difficulty in swallowing disappeared. The gait was for a time more ataxic than on entrance, but gradually improved until on discharge he walked quite well but he still had a definite ataxia. His reflexes varied a good deal. The patellar reflexes remained hyperactive, but on some days the left was more active than the right and *vice versa*. He developed a slight but definite rigidity of his right lower limb,

but this too disappeared before discharge. At times his arms felt weak, at times strong. They had regained a good deal of power before discharge, so that dynamometer readings showed 130 kg. with the right hand and 125 kg. with the left. He showed a good deal of emotional instability, laughing spontaneously with no provocation. His writing even up to a few days before discharge was extremely tremulous, and shortly before discharge he developed again numbness in his left side.

The patient showed no definite and steady improvement in any one way during his stay in the hospital, but rather a tendency to clear up in one respect only to have old symptoms and signs recur. His condition upon discharge may best be described probably as merely a mitigated state of his condition upon entrance.

Comment. While there has been much careful work on the pathology in the brain following carbon monoxid poisoning, there have been very few observations on the nonfatal cases of carbon monoxid poisoning. Stewart¹ reported a case of poisoning with carbon monoxid which showed bilateral softening in the corpus striatum and involvement by softening and hemorrhage of the deeper layers of the cortex, of the cerebellum, and of other parts of the brain. While most of the damage was in the corpus striatum, there was definite evidence of injury in other portions of the brain. Stoeper² found lesions in the cortex and cerebellum, with very decided softening in the lenticular nucleus. Ruge,³ in 1922, made a very interesting contribution. He studied 12 cases of carbon monoxid poisoning and concluded that softening and changes in the vessels occurred typically in the lenticular nuclei in carbon monoxid poisoning. In cases of moderately severe poisoning he found that fatty degeneration occurs in the ganglion cells twenty-four hours after poisoning, together with small hemorrhages into the perivascular spaces. After two days there occurs softening in the lenticular nuclei, but this is not well marked until four or five days after the injury. Ruge believes that injury to the nerve cell is the primary process, and that the thrombosis which is so commonly found in carbon monoxid poisoning follows upon this. Others have reported on the softening of the lenticular nuclei which is so commonly found in this condition, without, however, pointing out that there is at the same time a diffuse, wide-spread parenchymatous degeneration throughout the whole cerebrospinal axis. This was pointed out by Stewart,¹ by Ruge,³ Pineas,⁴ Poellchen⁵ and others.

It is difficult of course to correlate the findings in a case of carbon monoxid poisoning as reported in our patient in whom the injury was so slight, with the pathological findings as described in the literature. It is of more importance probably to record the findings as indicative of a slight degree of poisoning. This alone can be scientific when no postmortem proof is at hand. On the other hand, a study of the findings in our case reveals the fact that while

there were symptoms and signs of involvement of the lenticular nuclei, not all the findings could be explained on the basis of pathology in this area though most of them are explainable on this basis. The weakness of the upper extremity, the rigidity—moderate to be sure—in first one lower extremity and then the other, the increased reflexes in the lower extremities, together with the difficulty in swallowing and the stiff gait, suggest an interference with pyramidal tract conduction and with the bulbar nuclei. Very likely the amount of injury which was produced was probably no more than Ruge describes as taking place twenty-four hours after moderately severe poisoning, namely, a fatty degeneration in the ganglion cells; or even less than this may have occurred. Certainly no very severe injury to the lenticular nuclei could have been possible for the signs were never very marked. Particularly interesting was the shifting of physical signs, of weakness first in one arm, then in another, and of stiffness in alternate legs. The difficulty which the patient had in swallowing was a real one, and often resulted in the inability to swallow liquid foods. This had practically completely disappeared on discharge.

The unsteadiness of gait and the incoördination of the arms and legs might be explained by the presence of a peripheral neuritis which has been shown by Wilson and Winkelman⁶ to be present in cases of carbon monoxid poisoning. On the other hand, there never were signs of a peripheral nerve inflammation, and the type of asynergia which the patient showed was definitely of a cerebellar type. One might venture the opinion that they were due to involvement of the cerebellum either by punctate hemorrhage, or by involvement of the ganglion cells. Headache, which has been described by Forbes, Cobb and Fremont-Smith⁷ as an early symptom in carbon monoxid poisoning, was present but a very short time and was not very severe. These authors have pointed out also that carbon monoxide poisoning in the experimental animal is followed by cerebral edema. They do not state, however, how long the edema persists, and what may be its results, besides headache.

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THE EFFECT OF SPLEEN EXTRACT AND BONE MARROW ON THE BLOOD PICTURE IN PULMONARY TUBERCULOSIS.

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THE work done by Leake and Evans, of the University of Wisconsin, on spleen extract and bone marrow in the treatment of secondary anemia seems to furnish a tangible means with which to improve the blood picture in the various types of secondary anemias. In a recent article¹ they describe the results obtained by them in the treatment of anemia by the oral administration of spleen extract and bone marrow in capsule form, principally in general medical and surgical cases. They² believed that there must be some reserve in the body for the blood constituent and felt that stimulation of the bone marrow would cause a rapid production of erythrocytes and a corresponding increase in the hemoglobin content, the bone marrow being the reservoir for the cellular elements of the blood.

Fisher and Snell,³ of the National Military Hospital, Milwaukee, recently published a report of 28 cases whose anemias were treated with this preparation. Twenty-two of these cases showed definite improvement in the blood picture.

Reference can be made to a recent article⁴ published by the writer in which a series of 23 cases, suffering from active pulmonary tuberculosis were treated, 21 of whom showed a definite improvement in the blood picture.

A desire to confirm these results lead to the selection of another group of 23 cases, using the blood picture as the index for making selections. These were all cases of active pulmonary tuberculosis. Spleen extract and bone marrow* was administered to these patients in capsule form three times daily, a half hour before meals after a control period of one month. Weekly counts were made on each patient during the one-month period of control and also during the two-months period of treatment. Only a moderate amount of improvement resulted during the control period; but during the period of treatment a marked rapid rise in the hemoglobin percentage and red cells was obtained.

All hemoglobin determinations were made with a Bausch and Lomb colorimeter and the Max Levy hemocytometer used in counting the cells. One technician† was engaged in the work, making the percentage of error constant.

As objective criteria of improvement the rule used by Leake and Evans⁵ was followed. They state that "If the hemoglobin percentage did not improve by 5 points nor the erythrocyte count by 250,000

* The spleen marrow used in this investigation was prepared by the Wilson Laboratories, Chicago.

† I wish to express my appreciation of the careful technical work done by our laboratory technician, Miss Anna E. Ryan.

cells, the case was classed as showing no improvement. An increase in the hemoglobin percentage between 5 and 10 points and in the red blood cells between 250,000 and 500,000 placed the case in slightly improved class. If the hemoglobin percentage rose from 10 to 15 points and the erythrocyte count from 500,000 to 1,000,000 cells, the case was noted as moderately improved. An increase in a patient of over 15 points in hemoglobin percentage and over 1,000,000 in the red cell count was considered as markedly improved."

TABLE SHOWING EFFECT OF TREATMENT ON THE BLOOD PICTURE.*

Patient.	Degree of disease.	Period, weeks.	R.b.c. per cu. mm.	Hemoglobin, per cent.	
1 . . .	Far adv.	1	4,520,000	82	
		2	4,610,000	86	
		3	4,720,000	90	
		4	4,830,000	90	
		5	5,080,000	90	
		6	5,210,000	95	
		7	5,240,000	95	
		8	5,320,000	95	
		9	5,410,000	95	
		10	5,630,000	95	
		11	5,620,000	95	
		12	5,650,000	100	Markedly improved.
2 . . .	Far. adv.	1	2,950,000	50	
		2	3,020,000	55	
		3	3,020,000	57	
		4	3,020,000	58	
		5	3,500,000	62	
		6	3,470,000	65	
		7	3,930,000	70	
		8	3,900,000	75	
		9	3,970,000	75	
		10	3,990,000	75	
		11	4,000,000	75	
		12	4,140,000	75	Markedly improved.
3 . . .	Far adv.	1	4,930,000	80	
		2	5,020,000	85	
		3	4,840,000	85	
		4	4,870,000	85	
		5	5,070,000	90	
		6	5,470,000	95	
		7	5,540,000	95	
		8	5,500,000	95	
					Moderately improved and left institution against advice.
4 . . .	Mod. adv.	1	4,890,000	80	
		2	4,830,000	80	
		3	4,700,000	78	
		4	4,700,000	78	
		5	4,700,000	80	
		6	4,810,000	80	
		7	4,810,000	80	
		8	5,050,000	80	
		9	5,050,000	89	
		10	5,220,000	95	
		11	5,380,000	95	
		12	5,520,000	95	Moderately improved.

* The beginning of treatment, which was always after the fourth week, is indicated by a dash line.

396 DUNHAM: SPLEEN EXTRACT IN PULMONARY TUBERCULOSIS

Patient.	Degree of disease.	Period, weeks.	R.b.c. per cu. mm.	Hemoglobin, per cent.	
5	Far adv.	1	2,980,000	50	
		2	3,020,000	55	
		3	3,160,000	55	
		4	3,280,000	57	
		5	3,360,000	58	
		6	3,380,000	58	
		7	3,610,000	60	
		8	3,610,000	60	
		9	3,110,000	70	
		10	4,120,000	70	
		11	4,190,000	70	
		12	4,230,000	75	Markedly improved.
6	Far adv.	1	3,840,000	60	
		2	3,790,000	60	
		3	3,610,000	60	
		4	3,550,000	60	
		5	3,480,000	60	
		6	3,490,000	60	
		7	3,520,000	65	
		8	3,580,000	65	
		9	3,710,000	65	
		10	3,750,000	65	
		11	3,980,000	65	No improvement; left institution against advice.
7	Far adv.	1	3,280,000	55	
		2	3,000,000	55	
		3	3,330,000	55	
		4	3,520,000	56	
		5	3,320,000	50	
		6	3,330,000	50	
		7	3,380,000	55	
		8	3,390,000	55	
		9	3,400,000	60	
		10	3,440,000	60	
		11	3,490,000	60	
		12	3,500,000	60	No improvement.
8	Far adv.	1	4,950,000	80	
		2	4,840,000	78	
		3	4,890,000	80	
		4	4,890,000	80	
		5	5,260,000	85	
		6	5,550,000	95	
		7	5,590,000	95	
		8	5,640,000	100	
		9	5,680,000	105	
		10	5,670,000	105	
		11	5,650,000	110	
		12	5,650,000	110	Markedly improved.
9	Far adv.	1	4,370,000	80	
		2	4,330,000	77	
		3	4,330,000	80	
		4	4,330,000	75	
		5	4,720,000	75	
		6	4,700,000	75	
		7	4,530,000	75	
		8	4,700,000	80	
		9	5,040,000	80	
		10	5,050,000	80	
		11	5,070,000	85	
		12	5,070,000	85	Moderately improved

Patient.	Degree of disease.	Period, weeks.	R.b.c. per cu. mm.	Hemoglobin, per cent.	
10	Far adv.	1	4,850,000	84	
		2	4,780,000	83	
		3	4,780,000	83	
		4	4,780,000	82	
		5	5,040,000	80	
		6	5,260,000	85	
		7	5,230,000	90	
		8	5,250,000	95	Slightly improved; left institution without advice.
11	Mod. adv.	1	3,970,000	70	
		2	4,140,000	75	
		3	4,370,000	78	
		4	4,380,000	80	
		5	4,510,000	80	
		6	4,700,000	80	
		7	4,950,000	85	
		8	5,170,000	88	
		9	5,180,000	90	
		10	5,220,000	90	
		11	5,340,000	90	
		12	5,520,000	95	Markedly improved.
12	Far adv.	1	4,400,000	75	
		2	4,450,000	75	
		3	4,540,000	75	
		4	4,610,000	76	
		5	4,770,000	75	
		6	5,440,000	85	
		7	5,620,000	85	
		8	5,610,000	88	
		9	5,580,000	90	
		10	5,580,000	90	
		11	5,510,000	95	
		12	5,650,000	95	Markedly improved.
13	Far adv.	1	4,820,000	82	
		2	4,750,000	75	
		3	4,750,000	73	
		4	4,790,000	75	
		5	4,810,000	78	
		6	5,150,000	80	
		7	5,170,000	83	
		8	5,180,000	85	
		9	5,190,000	87	
		10	5,290,000	90	
		11	5,310,000	90	
		12	5,500,000	95	Moderately improved.
14	Mod. adv.	1	4,390,000	80	
		2	4,600,000	80	
		3	4,610,000	83	
		4	4,620,000	80	
		5	4,640,000	80	
		6	5,100,000	85	
		7	5,130,000	85	
		8	5,220,000	85	Moderately improved and left institution against advice.

398 DUNHAM: SPLEEN EXTRACT IN PULMONARY TUBERCULOSIS

Patient.	Degree of disease.	Period, weeks.	R.b.c. per cu. mm.	Hemoglobin. per cent.	
15	Far adv.	1	4,730,000	80	
		2	4,440,000	78	
		3	4,430,000	75	
		4	4,430,000	75	
		5	4,680,000	75	
		6	5,150,000	80	
		7	5,130,000	80	
		8	5,160,000	85	
		9	5,200,000	85	
		10	5,280,000	85	
		11	5,380,000	85	
		12	5,540,000	90	Slightly improved.
16*	Far adv.	1	4,170,000	80	
		2	4,090,000	80	
		3	4,410,000	80	
		4	4,470,000	80	
		5	4,660,000	85	
		6	4,660,000	85	
		7	4,950,000	88	
		8	5,160,000	90	
		9	5,160,000	90	
		10	5,270,000	92	
		11	5,270,000	92	
		12	5,290,000	95	Markedly improved.
17	Far adv.	1	5,100,000	85	
		2	5,030,000	82	
		3	5,010,000	80	
		4	4,930,000	80	
		5	4,960,000	80	
		6	5,440,000	85	
		7	5,490,000	90	
		8	5,540,000	90	
		9	5,510,000	95	
		10	5,510,000	95	
		11	5,670,000	95	
		12	5,670,000	100	Moderately improved.
18	Far adv.	1	4,580,000	80	
		2	4,460,000	80	
		3	4,460,000	80	
		4	4,770,000	80	
		5	4,980,000	90	
		6	5,150,000	90	
		7	5,140,000	90	
		8	5,210,000	90	
		9	5,250,000	90	
		10	5,400,000	90	
		11	5,460,000	95	
		12	5,460,000	95	Moderately improved.
19	Far adv.	1	4,630,000	80	
		2	5,040,000	90	
		3	5,030,000	90	
		4	5,240,000	90	
		5	5,330,000	90	
		6	5,520,000	90	
		7	5,540,000	90	
		8	5,620,000	95	
		9	5,610,000	98	
		10	5,680,000	100	Markedly improved; left institution against advice.

* Female.

Patient.	Degree of disease.	Period, weeks.	R.b.c. per cu. mm.	Hemoglobin, per cent.	
20	Mod. adv.	1	4,210,000	80	
		2	4,600,000	85	
		3	4,690,000	85	
		4	4,760,000	85	
		5	4,820,000	87	
		6	5,110,000	90	
		7	5,140,000	95	
		8	5,160,000	95	
		9	5,160,000	100	
		10	5,450,000	100	
		11	5,570,000	100	
		12	5,610,000	100	Markedly improved.
21	Mod. adv.	1	3,790,000	70	
		2	4,000,000	80	
		3	4,360,000	80	
		4	4,610,000	84	
		5	4,640,000	85	
		6	5,180,000	88	
		7	5,380,000	90	
		8	5,380,000	90	
		9	5,560,000	100	
		10	5,590,000	105	
		11	5,620,000	110	
		12	5,740,000	110	Markedly improved.
22	Far adv.	1	5,020,000	87	
		2	5,040,000	90	
		3	5,080,000	90	
		4	5,090,000	90	
		5	5,410,000	90	
		6	5,500,000	95	
		7	5,520,000	95	Slightly improved; left institution against advice.
23	Mod. adv.	1	4,050,000	80	
		2	4,330,000	80	
		3	4,460,000	83	
		4	4,890,000	88	
		5	5,260,000	90	
		6	5,550,000	92	
		7	5,550,000	97	
		8	5,620,000	100	
		9	5,630,000	105	
		10	5,670,000	110	
		11	5,690,000	110	
		12	5,790,000	110	Markedly improved.

There seems to be a variance of opinion among tuberculosis clinicians relative to the blood picture in tuberculosis. However, many clinicians have observed that a simple anemia is present in the majority of active cases of pulmonary tuberculosis; and it is quite generally conceded that in patients suffering from complications such as tuberculosis of the kidney or bladder, a definite secondary anemia is often present.

Pottinger⁶ has observed that the hemoglobin and red cells are usually diminished and present the picture of a simple anemia. Red cell counts and hemoglobin estimations were made on 261 cases at this institution and of the entire group only 38, or 14 per

cent showed the hemoglobin to be 90 per cent or above and the erythrocytes 4,800,000 or above.*

Schlomovitz⁷ in a recent publication showed conclusively by a comparison of relative blood cell volume in tuberculosis, that many a real anemia exists where apparently none was present. Fishberg⁸ has also noted that the hemoglobin percentage and red cell count is occasionally low; but believes that the condition is apt to occur most often in the early and late stages of the disease.

All data pertaining to the clinical course of the cases reported in this paper have been omitted, as the main object of this report is to show the effect of spleen extract and bone marrow upon hemoglobin and red cell production.

Thus far there are no data appearing in the literature pertaining to the effect this preparation has upon the clinical course of tuberculosis; and it is believed that observations of the effect of this preparation upon the clinical course of the disease should be made.

It would be interesting to read the reports by independent workers on the results obtained with this preparation in the treatment of tuberculosis.

Summary. 1. Twenty-three cases of active pulmonary tuberculosis are reported; 2 showed no improvement in the blood picture; 3 were slightly improved; 7 moderately improved and 11 were markedly improved, making a total of 21, or 91 per cent improved.

2. Spleen extract and bone marrow will definitely increase erythrocyte and hemoglobin production.

3. Further study of the use of this preparation in tuberculosis is indicated.

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* From the laboratories of the Oak Forest Tuberculosis Hospital.

A REPORT OF SIX CASES OF PYELITIS IN THE NEWLY-BORN INFANT.

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PYELITIS in the newly-born infant has generally been considered an uncommon disease. As far back as 1876, Huttenbrenner called attention to pyelitis in infants, but he referred more to older infants and young children. Since then, Escherich, Trumpp, Holt and others have reported pyelitis in older infants and young children. Göppert, in 1908, found pyelitis to be rare in the first three months of life. In 106 cases, 63 occurred in the first year of life and only 6 in the first three months. He estimates that about 1.2 per cent of his patients have pyelitis.

Pyelitis is probably much more prevalent in female than in male infants. Escherich, Göppert, Helmholtz, Grulee and Abt agree that the percentage of occurrence in females is high, ranging from 70 to 100. Schwartz concludes that actual bacilluria is twice as prevalent in girls as in boys. Helmholtz believes, however, that the ratio in newly-born infants is more nearly equal.

It is probable that all cases of pyelitis are caused by bacteria, which gain entrance to the mucosa and adjacent urinary parts as a result of a lowered resistance. The bacteria most commonly noted are *Staphylococcus pyogenes aureus* and *albus*, *streptococcus*, *colon bacillus*, *typhoid bacillus*, *tubercle bacillus*, and *pneumococcus*. In 1894, Escherich believed that the sole causative organism was *B. coli* and even named the condition "colecystitis." Helmholtz reports 45 cases, 36 girls and 9 boys; 36 cases showed *B. coli*, 1 *staphylococcus*, 2 *pneumococcus*, "1 *B. lactis aërogenes*, and 3 bacilli of the intermediate group of Gärtner." Hoppe believes that a vast majority of pyelitis cases are caused by *B. coli*. The fact that the majority of these pyelitic infections in older infants and children are girls having a *B. coli* infection suggests a contamination of the urethra with fecal material from a soiled diaper.

The following cases of pyelitis in newly-born infants have been observed.

Case Reports. CASE I.—Infant, L., male. This infant developed a temperature of 103.6° F. twelve hours after birth. This symptom was accompanied by restlessness and crying. At this time the urine obtained under as nearly as possible aseptic conditions showed 100 pus cells per c.mm. and a pure culture of *Staphylococcus pyogenes aureus*. During the second day, in spite of a 10-ounce

water intake the symptoms remained the same, with the temperature rising to 104° F. The blood count was hemoglobin 85 per cent, erythrocytes 5,200,000; leukocytes 12,600. Blood cultures from both mother and child were negative. A catheterized specimen showed 120 pus cells per c.mm. and a pure *Staphylococcus aureus* culture. The water intake was emphasized and the child alkalized. The temperature gradually subsided and the pus-cell count diminished until upon the seventh day the temperature was normal and the pus-cell count was only 2, with a negative culture. The symptoms entirely disappeared until the twenty-first day when there was a recurrence with symptoms of fever—100° to 101.6° F., restlessness and a urine cell count of 30, showing a pure culture of *Staphylococcus aureus*. The blood showed 12,000 white cells. These symptoms disappeared in four days and the child is now four months old and apparently normal.

CASE II.—Infant, M., female. This infant had a sharp rise of temperature to 102.6° F. on the third day. This was accompanied by restlessness and crying. Several catheterized specimens of urine showed pus cell counts from 100 to 150 and pure cultures of nonhemolytic streptococcus. The blood count was hemoglobin 90 per cent, erythrocytes 5,200,000, leukocytes 11,400. Blood cultures were negative. This child was put on treatment, and the findings steadily decreased and showed normal at the twelfth day. This child is now six months old. A good water intake has been maintained and the urine kept mildly alkalized. There has been no recurrence.

CASE III.—Infant, C., male, was premature two months; weight, 3½ pounds; incubator baby. There were apparently no abnormal findings. This infant developed a sudden temperature of 104.4° F. on the third day. The baby was very restless. The urine showed 250 pus cells per c.mm. and a pure culture of *B. coli*. Death occurred on the fourth day.

The following cases are from the service of Dr. Grulee at Presbyterian Hospital, Chicago:

CASE IV.—Infant, T., female. This infant suffered a rise in temperature on the third day to 100.6° F. accompanied by vomiting, which was at times projectile. In the absence of any physical findings, the urine was obtained under as nearly as possible aseptic conditions. The findings were 100 pus cells per c.mm. and a pure culture of *Staphylococcus aureus*. Repeated cultures gave the same results. The temperature subsided during the fourth day but there was a sudden elevation on the ninth day. The child left the hospital on the eleventh day. No further record is available.

CASE V.—Infant, O., male. This infant had an elevation of temperature on the third day to 100.6° F. He was regurgitating food, was very restless and cried a great deal. On the fifth day, the urine showed 400 pus cells per c.mm. and a nonhemolytic streptococcus. The symptoms of crying and vomiting continued although there was some improvement. When the child left the hospital on the tenth day, the urine still contained many pus cells and the cultures showed nonhemolytic streptococcus. No additional record is available.

CASE VI.—Infant, W., female. There was an elevation of temperature on the first day to 100° F. This slight fever continued nine days and was accompanied by regurgitation of food, vomiting and lifelessness. A urinalysis on the fourth day showed 3000 pus cells per c.mm. with a culture of *B. coli*. The blood count showed hemoglobin 85 per cent and leukocytes 16,500. These symptoms together with the urine findings were only moderately improved when the child left the hospital on the tenth day. No additional history is at hand.

The urine samples from these patients were secured either by catheterization or by using antiseptic precautions. Schwartz states that cultural growths from specimens obtained with sterile precautions are only slightly more frequent than those obtained by catheterization and that the latter is desirable but not essential. Kretschmer believes noncatheterized samples are inaccurate.

In this series, the first symptom noted in each case was an elevation of temperature ranging from 99° to 104° F. No local symptoms could be found on thorough examination, but in 4 of the cases there were rather marked restlessness and crying as if the infants were in distress. In 3 of the cases, regurgitation of food was noted. In none of the 6 cases was there any diarrhea, a condition so often reported preceding or attending pyelitis in older infants. Two of the patients were rather languid although at the same time irritable.

Contrary to the accepted finding that the large majority of the cases of pyelitis in older infants are females, this series in newly-born infants tends to strengthen the statement of Helmholtz that in newly-born infants the proportion is nearly equal. Of the 6 infants, 3 are male and 3 female. The causative bacteria in this series were twice *B. coli*, twice nonhemolytic streptococcus, and twice *Staphylococcus aureus*. This suggests that the overwhelming majority of *B. coli* infections such as is found in older infants is not present in the newly-born. Grulee has told me personally that he had 1 case of pyelitis in a newly-born infant showing a pure culture of *Bacillus pyocyaneus*.

That the fever usually has its onset about the second or third day, also suggests the possibility of an intra-uterine infection, or infection

at the time of birth. Case I might be interpreted as a congenital pyelitis. The leukocyte counts ranged from 11,000 to 16,000 figures which are not necessarily high for a newly-born infant.

The treatment used in this series was the one often followed. Sodium citrate, sodium bicarbonate, or equal parts of each were given with large amounts of water. With the exception of Case III, which was a premature baby, these patients all responded to this management. Their symptoms were relieved and the urine showed a rapidly decreasing pus-cell count. Practically all authorities agree that the one most important factor second to a correct diagnosis is the proper irrigation of the urinary passages through an increased intake of water. This may be given by mouth, by rectum, by hyperdermoclysis, intraperitoneally, or even by the intravenous route. In this series, it was not necessary to resort to any method other than by mouth. It is probably true that it is impossible to make the urine sufficiently alkaline so that it inhibits the growth of the *B. coli*. The curative properties of the alkaline medication may be due to the general alkalization and the diuretic effect.

Summary. 1. The incidence was the same in the two sexes in this series.

2. The infecting organisms in this series were *Staphylococcus aureus*, a nonhemolytic streptococcus and *B. coli*, each in 2 cases.

3. The time of onset suggests an invasion by the bacteria at the time of birth in most instances.

4. Case I suggests a congenital infection.

5. Leukocyte counts ranged from 11,000 to 16,000.

6. Blood cultures were negative.

7. These patients responded to alkalies and large quantities of water.

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THE PRACTICAL VALUE OF NEUTRAL RED AS A TEST FOR GASTRIC SECRETORY FUNCTION.*

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PREVIOUS to 1923, methods of testing the function of the stomach were based largely upon the administration of a test meal and the estimation of the quantity of acid and ferment in the stomach. At about this time several investigators in Europe attempted to test the stomach's ability to excrete certain dyestuffs. More recently others have advocated the use of dyes as a test for gastric function.

Neutral red as a clinical test for gastric function was suggested by Finkelstein¹ in the course of his investigations on the gastric excretion of dyes used in testing the function of the liver. Of 8 dyes tested, he found that only neutral red was excreted in the Pawlow pouch of a dog after subcutaneous injection. Fuld² had previously noted that neutral red appeared in the Pawlow pouch of a dog after the dye was introduced into the stomach proper. Later Glaessner and Wittgenstein³ applied this observation clinically in a series of 40 cases. Four cubic centimeters of a 1 per cent solution of neutral red was injected by them intramuscularly and the appearance time of the dye in relation to various states of gastric acidity noted. The appearance time in hyperacid cases was from seven to eight minutes, in normal cases from ten to fifteen minutes, in hypoacid cases twenty to sixty minutes, and in anacid cases the dye was not excreted. They also noted that the gastric mucosa showed a distinctly stained area around the pylorus, and expressed the opinion that the acid cells were principally concerned with the dye excretion. Saxl and Scherff⁴ investigated particularly the gastric excretion of methylene blue. They observed that the entire gastric mucosa was equally stained by the dye following its intravenous injection. These workers further noted that neutral red was secreted to a greater extent by the stomach than methylene blue. Neutral red injected into the peritoneum of a rat was not eliminated by any particular type of gastric cell, although the pyloric segment was more intensely stained with dye than the fundus.

Hirabayashi,⁵ in experimenting with gastric cannula dogs, found

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that the rate of excretion of neutral red depended upon the degree of stomach secretion as a whole, and that local lesions of the mucosa delayed and lowered the excretion of the dye. The stomach continued to eliminate dye after the hydrochloric acid was completely suppressed by silver-nitrate solution.

With the idea of attempting to ascertain the clinical adaptability of this method of testing gastric function, this work was undertaken. We have realized for some time the inadequacy of the fractional gastric analysis for determining accurately the presence of achylia gastrica. In this condition especially, the information gained from such analyses with regard to the secretory function of the stomach is not altogether reliable. Therefore, with the hope that the excretion of neutral red might prove a welcome addition to our diagnostic armamentarium in cases of this type, particularly the borderline cases of hyposecretion and anacidity, we have carried out this test in a number of patients, showing varied gastric conditions.

TABLE I.—APPEARANCE TIME OF NEUTRAL RED IN STOMACH FOLLOWING INTRAMUSCULAR INJECTION OF 40 MG. OF DYE.

Case No.	Acidity.	Appearance time of acid by fractional analysis.	Appearance time of dye.	
			Minutes.	Group average.
I . .	Hyper.	Present in fasting stomach	18	23 min.
II . .	Hyper.	Present in fasting stomach	30	
III . .	Hyper.	Present in fasting stomach	7	
IV . .	Hyper.	Present in fasting stomach	11	
V . .	Hyper.	Present in fasting stomach	15	
VI . .	Hyper.	30 to 40 min.	50	
VII . .	Hyper.	Present in fasting stomach	20	
VIII . .	Normal	Present in fasting stomach	30	14½ min.
IX . .	Normal	Present in fasting stomach	17	
X . .	Normal	Present in fasting stomach	9	
XI . .	Normal	Present in fasting stomach	15	
XII . .	Normal	Present in fasting stomach	5	
XIII . .	Normal	Present in fasting stomach	12	
XIV . .	Hypo.	45 min.	45	32 min.
XV . .	Hypo.	15 "	32	
XVI . .	Hypo.	45 "	30	
XVII . .	Hypo.	15 "	27	
XVIII . .	Hypo.	Present in fasting stomach	25	
XIX . .	Hypo.	60 min.	30	
XX . .	Hypo.	20 "	71	
XXI . .	Hypo.	45 "	45	
XXII . .	Hypo.	45 "	45	
XXIII . .	Hypo.	45 "	20	
XXIV . .	Hypo.	Present in fasting stomach	12	
XXV . .	Hypo.	Present in fasting stomach	20	
XXVI . .	Hypo.	45 min.	12	
XXVII . .	Hypo.	Present in fasting stomach	60	
XXVIII . .	Hypo.	Present in fasting stomach	10	
XXIX . .	Hypo.	15 min.	6	
XXX . .	Hypo.	45 "	15	
			60	

Appearance Time in the Stomach following Intramuscular Injection. In the first series of cases tested, the following technic was employed: The patient reported after a twelve-hour fast. An ordinary gastroduodenal tube was passed into the stomach and the residuum withdrawn. Four cubic centimeters of a 1 per cent solution of neutral red (40 mg.) were injected intramuscularly into the gluteal region. Water was given by mouth and a steady drip established from the duodenal tube. The first faint pink color in the gastric contents thus obtained, was recorded as the appearance time of the dye.

Thirty cases were examined in this way. They were divided into 3 subgroups according to the degree of acidity: hyperacid, normacid and hypoacid (Table I). The appearance time of the dye in 7 cases of hyperacidity ranged from seven to fifty minutes with an average of twenty-three minutes. In the normacid group of 6 cases the appearance time was from five to thirty minutes with a group average of fourteen minutes. Seventeen cases of subacidity had an appearance time of from six to seventy-one minutes, averaging thirty-two minutes to the group. The hypoacid cases as a group show a greatly delayed appearance time of the dye. The normacid stomachs secrete the dye more rapidly than the hyperacid group. The small number of cases in these last 2 groups make any definite conclusion as to the relative appearance time for these groups impossible.

Quantitative Intramuscular Method. An estimation of the amount of dye secreted by the stomach in two hours was attempted on a series of cases. The method used was first suggested by Davidson of Boston, who is working with neutral red in cases of pernicious anemia.

Using the same amount of dye, injected in the same manner as given above, and with the patient lying on the left side, 50-cc quantities of water were introduced into the stomach through the tube at fifteen-minute intervals. The water was drained into a series of bottles over a period of two hours.

The appearance time of the dye was noted. The quantity of liquid obtained from the stomach during each fifteen-minute interval was then subjected to a colorimetric determination as follows:

Each fifteen-minute return was diluted to 100 cc with water and poured into a test tube of large diameter. Standards were made by dissolving accurately weighed amounts of neutral red in water. The dilutions ranged from 1 to 8,000,000 to 1 to 100,000, representing 0.00013 gm. to 0.001 gm. respectively in 100 cc of water. These dilutions were placed in standard size large caliber test tubes for comparison. The gastric juice does not alter the color of the dye in any way and accurate comparisons are possible. The standards should be freshly prepared every six weeks.

Twenty-two cases are included in this quantitative series (Table II). They have been classified according to the degree of gastric

acidity. Five hyperacid cases had an average elimination of 0.0676 mg. of dye in two hours after the injection of the 40 mg. of neutral red. One of these cases had practically no elimination, although a hyperacid curve was obtained from the gastric analysis. Only 3 cases having normal acidity were tested; the group average was 0.1313 mg., or twice that of the hyperacid cases. The average secretion for the group of low acid cases was 0.0387 mg., considerably below either of the other groups. The dye appeared as a faint trace in 6 cases. These cases had extremely low acidities or very much delayed appearance time of hydrochloric acid secretion following the test meal. The greater proportion of dye was eliminated during the first hour.

TABLE II.—QUANTITATIVE ELIMINATION OF NEUTRAL RED IN THE STOMACH FOLLOWING INTRAMUSCULAR INJECTIONS OF 40 MG.

OF DYE.			
Case No.	Degree of acidity.	Neutral red excreted in 2 hrs., mg.	Group average acid excretion, mg.
I	Hyper.	Estimation not possible	Hyper., 0.0676.
II	Hyper.	0.0705	
III	Hyper.	Very faint trace	
IV	Hyper.	0.1035	
V	Hyper.	0.0963	
VI	Normal	0.0598	Normal, 0.1313.
VII	Normal	0.2401	
VIII	Normal	0.0598	
IX	Hypo.	Faint trace	Hypo., 0.0387.
X	Hypo.	0.0307	
XI	Hypo.	Faint trace	
XII	Hypo.	0.030	
XIII	Hypo.	0.112	
XIV	Hypo.	0.143	
XV	Hypo.	Faint trace	
XVI	Hypo.	Faint trace	
XVII	Hypo.	0.0809	
XVIII	Hypo.	Faint trace	
XIX	Hypo.	0.0083	
XX	Hypo.	Faint trace and bile	
XXI	Hypo.	0.0663	

The following conclusions are warranted from this study of the quantitative technic following the 40 mg. intramuscular dose.

1. Only 0.25 per cent of the neutral red introduced was obtained from the stomach in the normacid cases. The quantity is so infinitesimal that a quantitative estimation of the amount is of little value.

2. The hyperacid group has a lower dye excretion than the normal acid group. The same result was found in testing for appearance time only.

3. It is only in the markedly reduced acidities that the test seems to be of value.

Intravenous Injection of 125 mg. of Dye. The small amount of dye excreted following a 40-mg. dose injected intramuscularly led us to try larger amounts of dye intravenously.

Dr. John A. Kolmer very kindly tested out the toxicity of neutral red on rabbits. He reported that it was well borne in the dose of 0.1 gm. per kilogram of body weight. He found that 0.2 gm. would kill the animal immediately, and reported 0.140 gm. as the maximum tolerated dose. If human beings were of equal susceptibility this would mean that an individual weighing 70 kg. could stand about 9.8 gm.

Five hundred milligrams were injected intravenously in 3 cases. The return was instantaneous and the amount of dye was sufficient to color each return a deep red. The patients suffered untoward effects, notably cough, dyspnea, vomiting and generalized discomfort. Three cases were given 250 mg., and the dye elimination was still considered excessive. It was found that 125 mg. of dye was the most suitable dose. The technic followed was the same as that referred to under the quantitative intramuscular method, except that 125 mg. of neutral red dissolved in 5 cc of sterile water were injected into a vein followed by 5 cc of normal salt solution.

Appearance Time following Intravenous Method. The appearance time of the dye following the injection of 125 mg. of dye intravenously was recorded in 19 cases (Table III). Three cases of hyperacidity had an average appearance time of four minutes; six minutes was the group average for 3 normacid cases. Thirteen cases of hypoacidity (not including achylia) had an average appearance time of fourteen minutes after the injection. The intravenous injection of the dye produces a more rapid appearance time than the intramuscular injection (Table I).

As a rule the higher the acidity, the more rapidly the dye appeared in the stomach. This is not specifically true in each instance, for example, in 5 cases of low acidity the dye was present in less than eight minutes. Two of these cases had an appearance time of four minutes; the average for the hyperacid group. All of the normal and hyperacid cases had dye in the stomach in eight minutes or less after injection. Two cases classified as hypoacidity but having gastric enzyme had dye in the stomach in four and seven minutes (Cases XIII and XVII). It is obvious that the appearance time of dye in the stomach does not depend solely upon the degree of acidity nor the appearance time of acid following a test meal, and cannot be depended upon as a test for gastric secretion.

Quantitative Elimination: Intravenous Method. Three hyperacid stomachs after the intravenous injection of 125 mg. of dye, eliminated on an average 2.393 mg. of dye in two hours (Table III). The average excretion for 3 normacid cases was 1.699 mg. of dye. Thirteen cases of hypoacidity had an average elimination of 0.353 mg. In this series there was a crude ratio maintained between the degree of acidity and the amount of dye excreted by the stomach. This ratio is more constant than the ratio between the appearance time of the dye and the degree of acidity. The normacid cases

excreted only 1.2 per cent of the dye injected in two hours. This represents a very small percentage of dye excretion by the stomach. That the dye is largely eliminated by other organs than the stomach is obvious. Consequently, little reliance can be placed upon any quantitative method of testing the secretory function of the stomach by this dye.

TABLE III.—APPEARANCE TIME AND QUANTITATIVE ELIMINATION OF NEUTRAL RED IN THE STOMACH FOLLOWING INTRAVENOUS INJECTIONS OF 125 MG. OF DYE.

Case No.	Acidity.	Appearance time of acid in fractional gastric analyses.	Appearance time of dye, min.	Dye eliminated in 2 hours, mg.	Average appearance time, min.	Average dye, mg.
I . . .	Hyper.	Fasting	4	2.717	4	2.393
II . . .	Hyper.	Fasting	4	3.486		
III . . .	Hyper.	Fasting	4	0.976		
IV . . .	Normal	Fasting	8	1.434	6	1.699
V . . .	Normal	Fasting	5	0.644		
VI . . .	Normal	Fasting	5	3.019		
VII . . .	Hypo.	Fasting	15	0.230	14	0.353
VIII . . .	Hypo.	None	8	1.38		
IX . . .	Hypo.	45 min.	16	0.283		
X . . .	Hypo.	Fasting	7	0.018		
XI . . .	Hypo.	None in 45 histamin	12	0.751		
XII . . .	Hypo.	45 min.	5	0.221		
XIII . . .	Hypo.	None; histamin	7	0.025		
XIV . . .	Hypo.	30 min.	4	0.797		
XV . . .	Hypo.	None	45	Trace		
XVI . . .	Hypo.	None	35	Trace		
XVII . . .	Hypo.	None	4	0.289		
XVIII . . .	Hypo.	None	6	0.596		
XIX . . .	Hypo.	None	15	Trace		

Cases of True and Questionable Achylia Gastrica. A series of 20 cases suspected of having achylia gastrica were examined (Tables IV and V). Eleven of these cases failed to show dye in the stomach following either the intravenous or the intramuscular injection, or both (Table IV). Two cases were examined by the intravenous method only, 5 by both methods, and 4 by the intramuscular method. Five of them had no secretory response following an injection of histamin. The remaining cases were not examined by the histamin method, but repeated gastric analyses over a considerable period of time consistently demonstrated the absence of both acid and enzyme. In Case VIII, both methods were carried out. By the intravenous method an appreciable amount of flocculent material was present in the second bottle (thirty to forty-five

minutes extraction). When the acid was added to this sediment it was colored a faint pink. The sediment microscopically was found to consist of cellular matter probably exfoliated from the duodenum. Two cases (I and III) had a trace of bile regurgitated into the stomach in one of the extractions. These bottles containing a trace of bile also contained a small amount of dye, after adding hydrochloric acid.

TABLE IV.—THE RESULTS OF INTRAMUSCULAR AND INTRAVENOUS INJECTIONS OF NEUTRAL RED IN TRUE ACHYLIA GASTRICA.

Case No.	Acid and enzymes in fractional analyses.	Gastric secretion after histamin injections.	Dye found after intramuscular injections of 40 mg. neutral red.	Dye found after intravenous injections of 125 mg. neutral red.
I . . .	Negative	Not done	None	None
II . . .	Negative	Negative	None	None
III . . .	Negative	Not done	None	None
IV . . .	Negative	Not done	None	None
V . . .	Negative	Not done	None	None
VI . . .	Negative	Negative	None	None
VII . . .	Negative	Negative	None	None
VIII . . .	Negative	Negative	None	None
IX . . .	Negative	Negative	None	None
X . . .	Negative	Negative	None	None
XI . . .	Negative	Negative	None	None

TABLE V.—THE RESULT OF INTRAMUSCULAR AND INTRAVENOUS INJECTIONS OF NEUTRAL RED IN QUESTIONABLE AND TRUE ACHYLIA GASTRICA.

Case No.	HCl in fractional gastric analyses.	Rennet in fractional gastric analyses.	Gastric secretion after histamin injections.	Dye found after intramuscular injections of 40 mg. of neutral red.	Dye found after intravenous injections of neutral red.
I . .	Negative, 1; present, 2	Negative, 1; present, 2	Not done	Trace	
II . .	Repeatedly absent	Present, 1	Acid present	Trace	Dye appeared in 7 min.; small amount.
III . .	Negative, 1; low, 2	Negative, 1; present, 2	Acid present	Moderate amount	Dye appeared in 5 min.; normal amt.
IV . .	Repeatedly absent	Repeatedly absent	Acid and rennet present	None	Dye appeared in 12 min.; moderate amount.
V . .	Repeatedly absent	Repeatedly absent	Acid negative; rennet present	None	Dye appeared in 8 min.; moderate amt.
VI . .	Absent	Present	Not done	Not done	Dye appeared in 15 min.; trace.
VII . .	Repeatedly absent	Present	Not done	Not done	Dye appeared in 6 min.; moderate amt.
VIII . .	Repeatedly absent	Negative, 1; present, 2	Not done	Not done	Dye appeared in 4 min.; moderate amt.
IX . .	Absent	Negative	Not done	Not done	Dye appeared in 35 min.; trace.

Table V includes a series of 9 very instructive cases. They were considered to be achylia at some time previous to the neutral red test. In 3 cases (IV, V and IX), both acid and enzyme were repeatedly absent after fractional gastric analyses. Cases IV and V had either acid or enzyme after histamin injection. The intramuscular injection of 40 mg. of dye failed to cause excretion by the stomach in these 2 cases. Following the injection of 125 mg. of dye intravenously, a considerable amount of dye appeared in the stomach. These 2 cases cannot be classified as instances of true achylia gastrica, because of response to histamin. The intramuscular dose of 40 mg. proved insufficient to produce neutral red excretion. The intravenous method is superior to the intramuscular technic in suspected cases of achylia gastrica. The neutral-red test, however, cannot be held superior to the injection of histamin for the same purpose. Indeed, it is less satisfactory because of the possibility of dye regurgitation into the stomach from the duodenum in achylia gastrica cases. In 4 cases in which histamin caused acid and enzyme response, dye was extracted from the stomach following the injection of 125 mg. intravenously. Case V had enzyme but no acid, even after histamin injections, yet dye appeared following intravenous injection. This rather excludes the acid cells as the only excretory cells for neutral red.

Excretion of Dye by Other Organs. Every case upon which the neutral-red test was performed was instructed to expectorate saliva into a basin. The saliva was examined for dye by adding hydrochloric acid, and it was found to be invariably absent. At the end of the two-hour test, the tube was removed and the patient asked to urinate. The urine was deeply colored by dye in every instance. In the cases in which little or no dye was obtained from the stomach, more dye was secreted in the urine. The dye was also present in the stools following neutral-red injections.

Animal Experiments. A short time after the clinical work on neutral red was started, it was obvious that animal experiments were necessary in order to determine the exact location of neutral red in the body following injection. It was decided to determine if possible, which cells in the stomach secreted the dye, and also what other organs took part in its elimination. These experiments were carried out in the Pathological Laboratories of the Graduate School of Medicine of the University of Pennsylvania, through the kind assistance and coöperation of Dr. Fred Boerner.

EXPERIMENT 1. Ten milligrams of neutral red were injected into the ear vein of a rabbit after the animal's abdomen had been opened and the pylorus clamped to prevent regurgitation of bile into the stomach. The animal was killed thirty minutes after injection. Dye could not be found in any of the viscera of the rabbit. It was found necessary to use a much larger dose in order to cause sufficient staining of the cells.

EXPERIMENT 2. The same procedure was carried out using 100 mg. of dye. The animal was killed after forty minutes. The dye was distinctly perceptible in the urine and bile from the gall bladder. The kidneys, liver and small intestines were stained with dye. The salivary glands did not contain dye. The stomach mucosa was stained a deep pink color throughout. There was a zone extending up from the pylorus for a distance of about 2 inches, which was more deeply stained and also a concentric ring of deep red about $\frac{1}{2}$ inch below the cardia. The duodenal mucosa was stained to a lesser degree than the mucosa of the stomach. Frozen sections were prepared from various levels of the stomach. Sections taken from all parts of the stomach showed dye distributed in the mucosa and submucosa. There was no difference in the degree of staining in any particular group of cells. All cells seemed to be stained equally. In spite of the large amount of dye injected the cells appeared only slightly tinted after frozen section.

EXPERIMENT 3. The same procedure was carried out on a cat weighing 8 pounds. The organs resembled grossly those of the rabbit with regard to the dye content with one exception. The first 12 inches of the mucosa of the small intestines were injected much deeper with dye than the stomach mucosa. The difference in degree of staining was marked. The duodenum just below the pylorus was a deep red for a distance of 6 inches, a lighter yellowish red for 6 inches which merged into a pink tint. The stomach mucosa was a pink tint throughout. The cat proved to be an unsatisfactory animal for experiment due to its frightened condition before and after injection. It was thought possible that the animal may have had a temporary suppression of gastric secretion due to fear. Although comparative histologists do not describe any difference in cell distribution in the cat, it was deemed advisable to test the excretion of neutral red in an omnivorous animal as well.

EXPERIMENT 4. One hundred milligrams of neutral red were injected into the ear vein of a pig weighing 17 pounds, without unduly exciting the animal. The pig was then allowed to drink water after the injection. One half hour later he was killed by a blow in the head followed by bleeding. Anesthesia was not used. Upon examining the viscera, the lower 2 inches of the stomach serosa and the whole of the small intestine were distinctly colored by the dye. The serosa of the terminal 3 feet of ileum was a deep pink color. The remainder of the small bowel showed a lighter pink and the antral portion of the stomach a very light pink. The pancreas and all of the lymph glands were pink in color, more particularly the mesenteric nodes. The salivary glands, trachea, bronchi, lungs, aorta, heart muscles and skin were not stained. Deep red dye was present in the urinary bladder, gall bladder and bile channels. The cut surface of the kidney and liver contained dye. Dye was squeezed out of the ampulla of Vater.

The mucosa of the gastrointestinal tract was exposed. The stomach was stained a deep pink color throughout, distinctly more so proximal to the pylorus for a distance of $1\frac{1}{2}$ inches. There was a sharp line of demarcation, about $\frac{1}{2}$ inch below the cardia, where the pink staining of the mucosa began. Free dye was present, mixed with a small quantity of food in the stomach. The mucosa of the whole of the small intestine was pink, but to a lesser extent than that of the stomach. From a distinct pink the color merged into a yellowish pink below the ampulla for some distance, due undoubtedly to bile admixture. The staining of the mucosa stopped sharply at the ileocecal valve, the colon not being stained. Since the terminal ileum was much more distinctly stained than the upper part of the small intestine, it would appear that the staining was due to excretion by the cells and not to the presence of bile in the bowel.

These experiments justify the following conclusions.

1. Neutral red, when injected intravenously, is eliminated by the entire stomach mucosa and the whole of the small bowel to the ileocecal junction.

2. It is also eliminated in the bile and urine in much larger quantities than in the stomach.

3. It is not secreted in the saliva.

4. The lymphatic structures take it up quickly and the lymph-nodes become colored distinctly with the dye.

5. The whole glandulature of the stomach is active in the secretion of the dye although the antral portion is consistently deeper in color.

6. Animal experiments confirm the impression derived from clinical observation that the bulk of dye injected is not eliminated by the stomach.

The value of neutral red as a test for gastric secretion is largely confined to the diagnosis of achylia gastrica. We believe that the ordinary gastric analysis cannot be relied upon in diagnosing this condition. Several cases recorded were looked upon as cases of true achylia after repeated fractional gastric analyses. These cases, however, gave a secretory response to histamin, and neutral red was eliminated when injected intravenously.

It has been held by Hirabayashi that local lesions of the gastric mucosa produced experimentally can be recognized by this test, but in our experience no such conclusion can be drawn clinically. If our contention is correct that the dye is secreted by the whole glandulature of the stomach, it is unlikely that a circumscribed lesion of the mucosa will reduce the dye excretion sufficiently to cause a local lesion to be suspected. When the amount of dye is reduced, a differentiation between local lesion and hypoaclidity cannot be made.

Regurgitation of bile into the stomach interferes with the quantitative estimation of the dye. It is possible to precipitate the bile from the specimen by a method described by two of us,⁶ but some of the dye would be lost in the procedure as it is taken up by the filter

paper. For this reason little information can be obtained by this method in cases that have been subjected to gastroenterostomy. We have observed three such instances.

The elimination of neutral red by the stomach, whether injected intramuscularly or into a vein, is very roughly proportionate to the amount of acid secretion. The appearance time of the dye following the intramuscular and the intravenous injection, is somewhat parallel to the concentration of hydrochloric acid in the stomach. The parallelism is not constant, however, and it is only in the markedly reduced acidities that the results are fairly consistent. The quantitative estimation of the amount of dye eliminated over a two hour period is almost equally unreliable. This method, however, following the intravenous injection of the dye, seems to parallel more closely the acid curve than either the appearance time of the dye or the intramuscular quantitative method.

Neutral red or any other dye, injected either into muscles or veins, cannot supplant or be compared with the fractional gastric analysis as a test for gastric function as a whole. Rehfuess describes the latter test as a method of measuring gastric work, that is, both the secretory and the motor function of the stomach, the latter being frequently overlooked by critics of this method. The dye test measures only the secretory activity of the stomach.

Conclusions. 1. Only a small fraction of the amount of neutral red injected either intravenously or intramuscularly, is eliminated by the stomach. The entire glandulature of the stomach participates in this excretion.

2. The greater proportion of the dye is excreted by the liver, kidneys and small intestines.

3. There is a rough relationship between the amount of dye secreted and the time of its appearance and the degree of gastric acidity. In low-acid stomachs delayed secretion rate and diminished quantities are generally found.

4. Neutral red does not appear in the stomach in cases of true achylia gastrica except when carried there by duodenal regurgitation.

5. Neutral red can be looked upon only as an imperfect test for gastric function, since it furnishes no information as to the motor power of the stomach.

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UNUSUAL EOSINOPHILIA WITH SPLENOMEGALY (EOSINOPHILIC LEUKEMIA?) IN A CHILD AGED SIX YEARS.

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THE extreme rarity of this condition makes it desirable to report even single cases and compare them with the few already in the literature.

Case Report. R. Z. was first seen by me, February 16, 1924, at the age of six years. She was referred by a laryngologist because her general health seemed poor.

Previous History. She was the older of two children. Her family history was negative. Birth was normal. She was breast fed for nine months, and for three years following this had difficulty with feeding, with a tendency to diarrheal stools. She also suffered from infantile eczema. At the age of one year she had an attack of influenza complicated by bronchopneumonia. Following this she had frequent attacks of bronchitis and "head colds." At the age of two years her tonsils and adenoids were removed. However, the colds continued, and she had severe attacks of otitis media. Because of a continual running nose, a second tonsil and adenoid operation was performed one year ago.

Present Illness. For the past few months the child had been under treatment by a laryngologist for continued colds and nasal discharge. A pansinusitis had been demonstrated, and a vaccine composed of Staphylococcus aureus, pneumococcus Type IV and hemolytic streptococcus was administered, the patient having had nine injections during the past four weeks. The general condition seemed only slightly improved, and the nose continued running. The child's appetite was fair, bowels regular, she slept well, was bright and wide awake, but had a tendency to irritability. She did not have fever. Operation on the sinus was being considered, but the child's poor resistance and general lack of stamina prompted the surgeon to have a more complete physical examination made.

Physical Examination. This showed a child with a somewhat scrofulous habitus. Her weight was 40 pounds (average for age, $43\frac{1}{2}$), and height $42\frac{5}{8}$ inches (average for age, $43\frac{1}{2}$). Her general condition was good. The skin was distinctly pale, but showed no eruptions. The lips were thick; the nose showed mucopurulent discharge. The cervical lymph nodes were slightly enlarged. The teeth were excellent. Throat examination showed complete removal of tonsils. The chest revealed signs of old rickets, but the heart and lungs were normal. The abdomen was slightly prominent and the spleen was felt two fingers' breadth below the free border, freely movable and very hard. Liver felt three fingers' breadth

below the free border. The urine showed no sugar, albumin or indican. The von Pirquet test was negative. The Wassermann reaction was negative. The blood findings are given in table. As a result of these findings the stools were carefully searched for parasites, stools being sent to three different examiners. All examinations failed to reveal ova or parasites.

On March 20 the child was again seen and the history was carefully searched for a possible attack of trichinosis. The child had had no illness remotely resembling this. Close questioning showed that the spleen had been found much enlarged by Dr. L. E. Holt when the child was two years of age. No blood examinations had been made.

A blood smear on March 20, 1924, showed the results given in table.

On April 6 a complete blood examination by Dr. Nathan Rosen-thal showed the results in table.

The child was given 3 drops of Fowler's solution three times a day.

On April 26 she had distinctly larger lymph nodes in the neck, a few small palpable nodes in the axilla and the groin. The spleen and liver were unchanged. For the blood count on this day see table.

One month later the child came to the office on account of a cough which seemed suspicious of pertussis. On June 2, which was the last time I saw the child, she was seen in a definite attack of whooping cough. She was taken home and grew rapidly worse developing a bronchopneumonia with very marked cardiac failure which caused her death within a few days. No further blood examinations were made and no postmortem examination was performed.

Discussion. This case is noteworthy because of the very unusual blood findings: During the two and a half months that the child was under my observation the white blood cells varied from 14,800 to 25,600, the eosinophilic polynuclear cells varied between 37 and 64 per cent and eosinophilic myelocytes varied from 2 to 6.3 per cent. With this blood picture there was associated an enlarged spleen, enlarged liver and a slight general adenopathy. There was practically no anemia.

This syndrome is one of great rarity; I have been unable to find a report of any similar case occurring in a child, though four cases somewhat resembling this one have been reported in adults.

Under the title of "Persistent Eosinophilia with Hyperleukocytosis and Splenomegaly," H. Z. Giffin reports from the Mayo Clinic the case of a male, aged thirty-one years, first examined, March 11, 1913. He gave a history of some febrile illness eight years previously, since which time his health had been poor. For about a year he had suffered from pain in the left thorax and had had

attacks of edema which became generalized and severe one week before admission. Examination showed a marked generalized edema, ascites, spleen extending to the level of the iliac spine and moderate enlargement of axillary nodes. There was no nephritis. The blood Wassermann test was negative. The blood count is shown in table.

An excised lymph node showed a moderate inflammatory reaction: A marked endothelial hyperplasia was present; eosinophilic polymorphonuclear leukocytes were numerous and a few myelocytes were seen.

The patient improved somewhat, but as the splenomegaly and the anemia persisted a splenectomy was performed in 1914. Following this the general condition improved, but the white blood cell count rose to 97,000 and three years later to 211,000, the eosinophil cells varying from 75 to 90 per cent. The patient in 1918 developed pneumonia and empyema, from which he died. The spleen weighed 2110 gm. and had the macroscopical appearance seen in myelogenous leukemia. The spleen, the bone marrow and the lymph nodes showed great numbers of polynuclear eosinophil cells and few myelocytes.

In 1919 Louis Shapiro described a case under the title "Eosinophilic (Polymorphonuclear) Leukemia." The patient, a man aged forty-eight years, was under observation about a year, during which time he showed a splenomegaly, enlarged liver, glycosuria, slightly enlarged inguinal and epitrochlear lymph nodes. The Wassermann test was positive. His blood picture is shown in table.

The autopsy revealed spleen weighing 1268 gm., fatty liver, thrombus in the right heart ventricle. The bone marrow consisted of a mass of cells, eosinophilic myelocytes with myeloblasts predominating, there being no fat spaces whatever. Microscopically the spleen showed thrombosis of vessels with infarcts; Malpighian bodies were diminished; there was infiltration with eosinophilic leukocytes.

R. G. Stillman presented a man before the New York Academy of Medicine in 1912. The patient, aged twenty-seven years, complained of loss of weight and color and showed a general adenopathy and large liver and spleen. The blood picture is given in table.

The patient's later history could not be followed.

In an article headed "Existe-t-il une leucémie à eosinophiles?" Aubertin and Giroux report the case of an adult with chronic cardiac disease. The blood picture is given in table.

There was slight enlargement of the spleen and no increase in the size of the lymph nodes. The case was followed for many years, the blood findings remaining about the same. The case came to autopsy but no detailed findings are given.

BLOOD PICTURES IN EOSINOPHILIC LEUKEMIA(?)

Case.	Hemoglobin, per cent.	Red blood cells in millions.	Leukocytes in thousands.	Per cent.						Remarks.
				Polymorphonuclears.	Small lymphocytes.	Large lymphocytes.	Mononuclears.	Eosinophils.	Eos. myelocytes.	
My patient:										
Feb. 16, 1924	80	32	24	..	3	41		
Mar. 20	29	16	10	6	37		
Apr. 6	80	4.83	25.6	18.3	9.6		1.3	64	6.3	Platelets, 310,000 (Dr. Rosenthal)
Apr. 26	14.8	17	0.5	52	5	Basophils, 0.5 per cent.
Giffin's case	69	3.62	15.4	13	18.3	1	..	66.3	..	Basophils, 1.3 per cent.
Shapiro's case	87	4.74	17.9- 236	4- 32.5	1- 13	1- 4.5	1- 4.5	48.5- 86.5	3.5- 6.6	Basophils, 5 to 1.3 per cent; basophilic myelocytes, 1 per cent
Stillman's case	111- 165	3.8	4.2	..	0.8	69.8	1.8	Mesoblasts, 0.2 per cent; Eosinophil metamyelocytes, 19.4 per cent.
Aubertin's and Giroux's case	10- 26	19.75	3	1.25	11.25	65.75	0.75	

All of these cases show in common a chronic illness accompanied by enlargement of the liver and spleen, increase in the total number of white blood cells, varying from 10,000 to 236,000, and an increase in the eosinophilic polynuclear cells up to 86 per cent. In all of these cases moreover the ordinary conditions giving rise to eosinophilia can be excluded (parasites, skin disease, trichinosis, anaphylactic phenomena, asthma, and so forth). What is the status of these cases? Should they be classed as a form of leukemia or not? In favor of their belonging to this group of diseases is the persistent increase in the number of white blood cells, the increase in the size of the spleen, the enlargement of lymph nodes, the presence of myelocytes in the blood and in some of the tissues examined. Against their being considered leukemia is: (1) The very small number of immature cells in the circulating blood (in my case 6.3 per cent) and (2) the absence of severe anemia. This last fact certainly differentiates these cases sharply from the ordinary leukemias, as for example in Shapiro's case, where even when the white cells reached enormous numbers, the hemoglobin and the red blood cells were approximately normal. The absence of any hemorrhagic phenomena in these cases is also noteworthy.

In Giffin's case the highest total white count before splenectomy was 21,800, whereas three years after the operation counts as high as 211,000 were obtained, and this author is inclined to view this increase as a result of the splenectomy. However, in Shapiro's case the total count rose from 17,900 to 236,000 during the course

of a year without any operative interference whatever. In my case the highest recorded white blood cell count was 25,600, obtained while the child was afebrile and suffering only from a chronic sinusitis. In the light of the other cases the sinusitis would seem to have been secondary and to have persisted in spite of treatment because the child's constitution was undermined by the blood disease. It also seems likely that the child's rapid succumbing to the terminal pulmonary infection may be explained on the same basis.

Whether this case and the other cases described should be classed as leukemia or not remains a matter for argument. The important fact is this: There exists a definite clinical syndrome characterized by a chronic course with splenomegaly, great eosinophilia, persistent leukocytosis at times reaching leukemic proportions and relatively slight anemia. Such a clinical picture may moreover occur in childhood.

Summary. A unique case of extreme eosinophilia is described occurring in a girl, aged six years. During the two and a half months in which the child was under observation she showed a moderately enlarged spleen, slight general adenopathy, leukocytosis varying between 14,800 and 25,600, eosinophilic polymorphonuclear cells varying between 37 and 64 per cent and eosinophilic myelocytes present up to 6.3 per cent.

Four somewhat similar cases in adults are reported from the literature, two with autopsy.

The relation of this condition to leukemia is discussed.

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INCREASED PERMEABILITY OF VESSEL WALLS AS A FREQUENT CAUSE OF PULMONARY HEMORRHAGE.*

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BLOOD spitting is a frequent symptom of pulmonary disease, particularly pulmonary tuberculosis. A very large majority of all

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patients suffering from active pulmonary tuberculosis expectorate blood sometime during their illness.

It was formerly generally accepted that blood in the sputum meant a destruction of a portion of the wall of a pulmonary vessel, the variation in size of hemorrhages depending upon the size of the vessel in which the opening occurred.

More careful observation of tuberculous patients, however, shows that blood coming from the lungs does not always indicate the same underlying condition. Ulceration of the walls of vessels of some considerable size and rupture of aneurysmal dilatations in cavities occur now and then and cause severe or even fatal hemorrhages. Injury to the walls of tiny capillaries is also a frequent cause of bleeding; but the great majority of pulmonary hemorrhages which occur, evidently from their very nature, are not due to either of these causes. They usually occur and recur under certain conditions, the most common of which are changes in weather, the presence of acute respiratory infections and during the menstrual cycle. They are usually small in amount, consisting of only one or two mouthfuls, but sometimes they are more copious. They frequently persist over several days and are apt to recur when the same or similar conditions again arise. Many of them occur in the early morning hours.

A tendency for tuberculous patients to spit blood during the menstrual period has long been recognized. It has been spoken of as a vicarious menstruation. This, we now know, to be an incorrect explanation. This blood spitting is a part of the general increase in severity of symptoms which occurs at this time, and is undoubtedly due to increased pathologic activity in the tuberculous foci. In explaining this according to the theory of Jobling and Peterson,¹ we assume that prior to the time that the menstrual disturbance occurs the enzymes which are instrumental in breaking down the tuberculous tissue are bound by antienzymes. These latter are not specific. When the enzymes which accompany the menstrual cycle enter the blood stream then a portion of the antienzymes which are binding the former leave them and bind those which accompany menstruation. The former, released, cause increased activity in the tuberculous areas. This increased activity at times appears as increased permeability of the capillaries and results in the escape of blood.

Observations made by different observers, the staff of the Phipps Institute,² and more recently Walsh^{3, 4} and Montgomery⁵ have called attention to an apparent relationship between certain hemorrhages and the presence of pneumococci and other organisms causing acute respiratory infection. This is too well established now to be questioned. I have noted it frequently. I have seen two quite severe hemorrhages accompanying tonsillitis, and many accompany the common acute respiratory infections. The writer⁶

previously stated in describing this type of hemorrhage: "I look upon this type as being due to a congestion much the same as we see in pneumonia and heart lesions. Is it not possible, however, that it might be due to toxic action?" And later:⁷ "The theory of toxic action seems to me to be the one which offers the best explanation. Such types of hemorrhage rarely occur except where the disease is active. It is not at all improbable that the hemorrhage is part of a collateral inflammatory exudation."

Browning⁸ made a study of symptoms including hemorrhage in its relationship to changes in weather at the Pottenger Sanatorium, and he concluded that there was a definite relationship between their occurrence and barometric changes. Hemorrhages of all kinds are affected by weather conditions. Sudden marked changes from wet to dry, or from dry to wet, fog, sudden hot or cold spells are accompanied by an increase in incidence of blood spitting, which can be readily observed in institutions where a tuberculous population of 100 or more exists.

Recent advances in biophysics and studies on the physiology of the circulatory system suggests a rational explanation for some of the types of bleeding here discussed. Krogh⁹ has discussed the effect of capillary poisons which cause such a dilatation of the vessel walls as to permit of ready passage of the constituents of the blood into the tissues. Among substances classed as capillary poisons he mentions certain salts of gold and arsenic, histamin and sepsin. Doubtless there are many substances having such action. Clinical evidence shows that many acute respiratory infections are accompanied by blood spitting. The type of acute respiratory infections which have been common since the pandemic of influenza in 1918 have not only been the cause of blood spitting in many frankly tuberculous patients, but in some in whom I could find no evidence of active tuberculous disease. Either the poisons from the tubercle bacilli or the tuberculous process or that from the germs causing the acute infection could probably act as direct capillary poisons, or there could be an increased permeability of the vessel walls as a result of the increased activity of the local cells. The increased local activity in this type may also be accounted for by the same enzyme-antienzyme action as mentioned in connection with menstruation.

Increased activity is accompanied by an increased permeability of tissues (Lilly^{10, 11} and Mathews¹²), so it is quite easy to understand how infections and menstruation, by causing selective action upon the already diseased areas, may have a tendency to cause increased activity in the areas of infection. Cells which are injured are more sensitive than normal cells, consequently an amount of stimulation which is not sufficient to affect normal cells might easily produce effects in cells which previously have been sensitized

by disease so as to cause such a degree of increased permeability as to allow the escape of blood or sanguineous fluid.

It is more difficult to explain the manner in which the blood spitting which accompanies changes in weather is produced. This inability to explain on our part is doubtless partly due to our ignorance of the effects upon the body caused by changes in weather and partly to a failure to appreciate the degree of physiologic adaptation which is required on the part of the body to preserve equilibrium during such changes, and especially to a failure to appreciate the handicap to adaptation which is experienced by those cells which are the seat of disease.

Think of the change that must be effected to cool the air from 120° , 200° and 300° , as is found in heated ovens, to 98.6° , the normal temperature of the body; or to warm it from zero or a -20° or 40° to that of the normal 98.6° of the body; or of saturating an air with moisture when its relative humidity is reduced to a minimum; or of the adjustment of the body that is necessary for it to function normally in both bright sunshine and in the presence of cloud. Think of the difference in stimulation that attends these various conditions, and the effects produced upon the vessels of the respiratory passages as a result of them.

The influence of the varying content in light rays and in electric units under conditions of storm and pleasant weather, and the changes in barometric pressure under the same conditions, are immense factors in disturbing physiologic action. The normal 14.7 pounds of pressure per square inch of body surface which is found at sea level changes enormously at these times. Huntington¹³ says the increase of 1 inch in barometric pressure is equivalent to adding a weight of 1,000,000 tons to each square mile of the earth's crust. This same relative change in pressure is experienced by the human body and means an additional ton of pressure. A decrease in barometric pressure removes weight in the same proportion. These changes call for enormous adjustment. Think what they mean to the superficial body structures and to mucous membranes.

Increased permeability shows itself most frequently in the bronchial mucous membranes, but it is also frequently noticed in the nasal mucous membrane when no apparent inflammatory condition is present.

The type of hemorrhages which depends on these weather changes is most apt to occur at the time of day when atmospheric pressure is low. There are two maximum and two minimum periods of atmospheric pressure each day, and it is interesting to note that the lowest pressure is found in the early morning (about 4 A.M.) hours, and that this is the time when most hemorrhages of this type occur. The second minimum occurs in the afternoon (about

4 P.M.), and this is another time in the day when hemorrhages occur.

According to biophysics, activity in body cells is an electric phenomenon brought about by a difference in potential between the two sides of the cell membrane. The point of injury or the point of stimulation of the cell assumes a negative charge, thus affording the condition necessary for starting an electric reaction. Increased electric reaction, increased cellular activity and increased tissue permeability are concomitant states which accompany action and reaction of tissues.

Summary. Acute infections of the lung are apt to produce their greatest effect at the point where the tissues are now or have been injured by tuberculous disease. This causes increased activity and permeability of tissues, including bloodvessels, which at times result in conditions which permit the passage of blood through the vessel walls.

The menstrual enzyme in some manner causes increased activity in local tuberculous processes, which is accompanied by increased permeability.

Certain weather changes, the exact factors in which we do not know, affect all tissues of the body, but particularly those of the lung which have been injured as a result of active disease, and cause the blood to pass through the capillaries. This is particularly true of those injured by tuberculous infection.

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OBSERVATIONS ON NONPOSTCICATRICIAL KELOID.

WITH A REPORT OF A CASE.

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LITERATURE records but very few exhaustively described cases of keloid (Geyer,¹ McKee,² Heidingsfeld,³ Freund⁴) that did not arise from a previously existing scar. The following case will prove of special interest, since the skin lesion was preceded by purpura.

Case Report. A. F., a white boy, aged four years, admitted to the Out-patient Department of the Children's Hospital on August 5, 1924, was complaining of a peculiar skin rash which appeared about six weeks previously to admission, following chickenpox. New lesions were still in the stage of development.

Family History. His two brothers were perfectly well. There was no history of asthma, eczema, tuberculosis, hyperthyroidism, lues, or hemophilia in the family.

Past History. The child was always in good health. He had had no diseases except measles, in March, 1923. On March 14, 1924, he was taken ill suddenly, the chief symptoms being fever (101°), sore throat and subcutaneous hemorrhages. He was admitted to the Children's Hospital with the diagnosis of purpura.

From the reports at that time the following facts are noted: A well-nourished boy. Temperature, 100.2°; pulse, 104; respirations, 23. On the right side of the forehead is a subcutaneous hemorrhage, the size of a silver dollar, with similar lesions on the right chest, under the right arm, over the abdomen and on the back. The tonsils are enlarged and cryptic. The heart, lungs and abdomen are negative; liver is not enlarged; the spleen not felt. There are no other evidence of hemorrhages (gums, urine, stool).

Laboratory data at that time included a blood count: Red blood cells, 3,743,000; leukocytes, 18,500; hemoglobin, 70 per cent; polymorphonuclears, 77 per cent; lymphocytes: small, 16 per cent; large, 7 per cent; platelets, 240,000; coagulation time, five minutes. Culture of throat, negative. von Pirquet and Wassermann tests, negative. Calcium content of blood, 8.9 per 100 cc. The urine showed no sugar, albumin or casts. During the time he was in the hospital symptomatic treatment was given, and tonsillectomy was performed on March 27. On March 31, when the patient was discharged, the fever had subsided and the hemorrhages were fading.

The patient felt perfectly well except for occasional pains which were described as colic-like; localized in the lower abdomen without association with bowel movement and food ingestion. They generally occurred during the night, and were not relieved by food. There was no abnormality of stool, no icterus, no nausea nor vomiting.

In the latter part of June the patient had chickenpox. The pustules appeared most thickly over the right and left thigh. While the typical lesions of chickenpox were disappearing there developed around them reddened areas from which scar-like elevations arose as seen on the day of admission. The patient came to the hospital for relief from mosquito bites from which he suffered three days previously.

Physical Findings. Temperature, 99.2°; pulse (rectal), 94; respirations, 20. Marked pallor of skin and mucous membranes; no signs of rickets. Eyes, ears, nose, sinuses, teeth and tongue are normal. The tonsillar areas show no diseased tissue left after tonsillectomy. Only the submaxillary glands show some enlargement but they are not tender. The thyroid is not felt. The heart and lungs are normal. The pulse is regular, full and of normal tension and volume. Blood pressure: systolic, 118; diastolic, 86. The abdomen, liver, spleen, genitalia and extremities are negative. The reflexes are normal.

Description of Cutaneous Lesions. 1. Over the right scapula there is a nevus pigmentosus of dark-brown color, the size of a dollar. (Fig. 1 A.)

2. There are a few blue and yellow maculæ on the back and stomach region which have the appearance of former hemorrhages. They are not hyperesthetic and do not show any involvement of the epidermis. (Fig. 1 C.)

3. On the exposed parts of the body, over both arms and legs, on neck and on the face are some inflamed areas from the center of which is a discharge of some serous fluid, such as seen in mosquito bites of two to three days' duration. They show a slow tendency to healing. On the right foot, around one of these areas, there is superficial edema of unusually large size. It extends from the middle of the foot over the ankles.

4. On the outside of both legs are peculiar lesions which at first inspection remind one of urticaria. There are numerous erythematous areas varying in size from that of a pea to that of a man's palm. They are not elevated, of violet-rose color and do not disappear on glass pressure. Their outline is not definite. There is no defect of the epidermis. Out of the largest areas scar-like formations arise, somewhat paler than the patient's skin, white on pressure and about 2 to 3 mm. elevated over the level of the skin. These scars are of a striking shape and different in all lesions. On the erythematous patch of the right upper leg the scar forms one

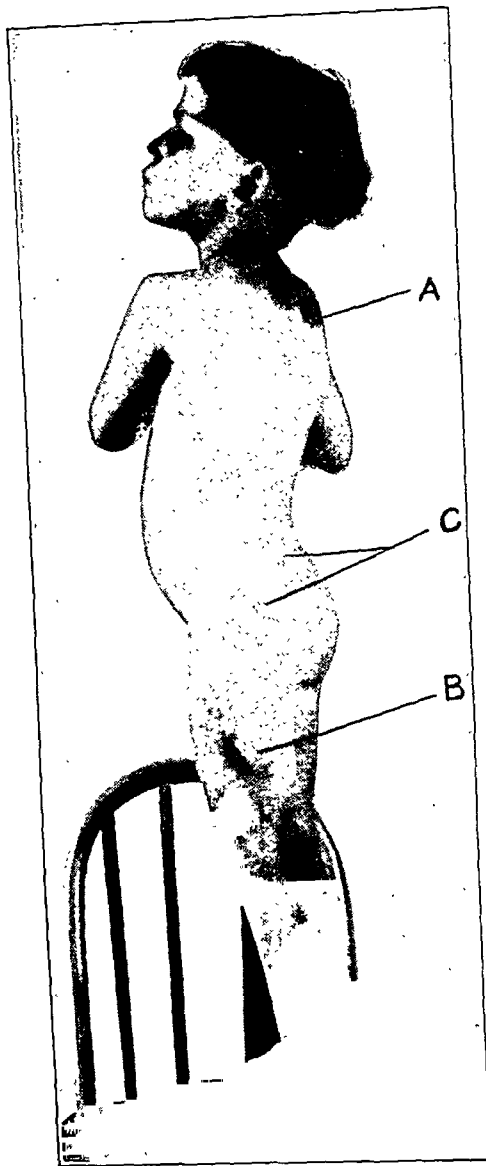


FIG. 1.—Photograph showing A, nevus; B, keloids; C, hyperpigmentations, residues of purpura.

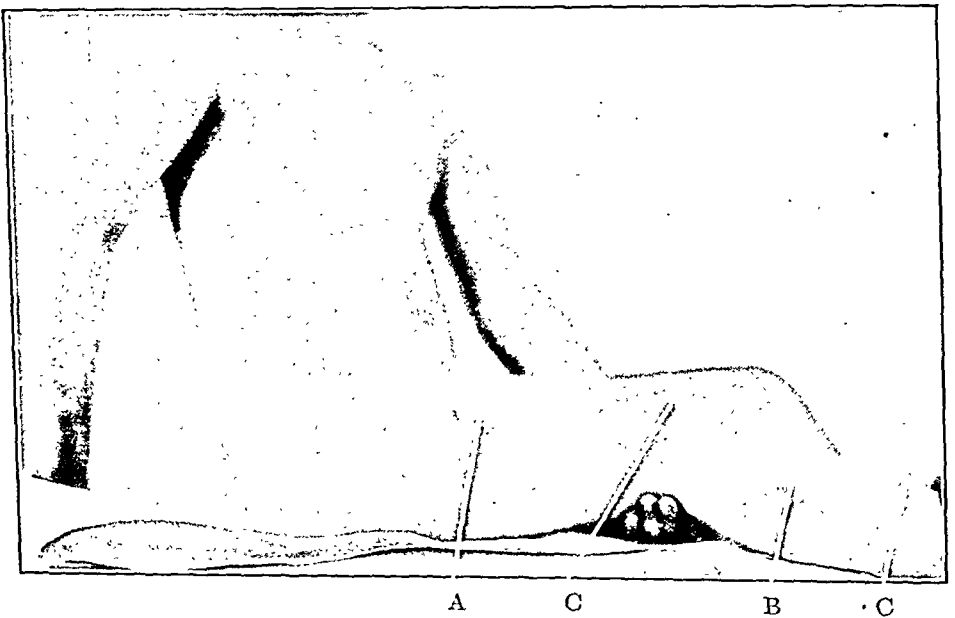


FIG. 2.—Keloids on right leg. A, showing transverse bifurcations; B, circular form; C, beginning growth.

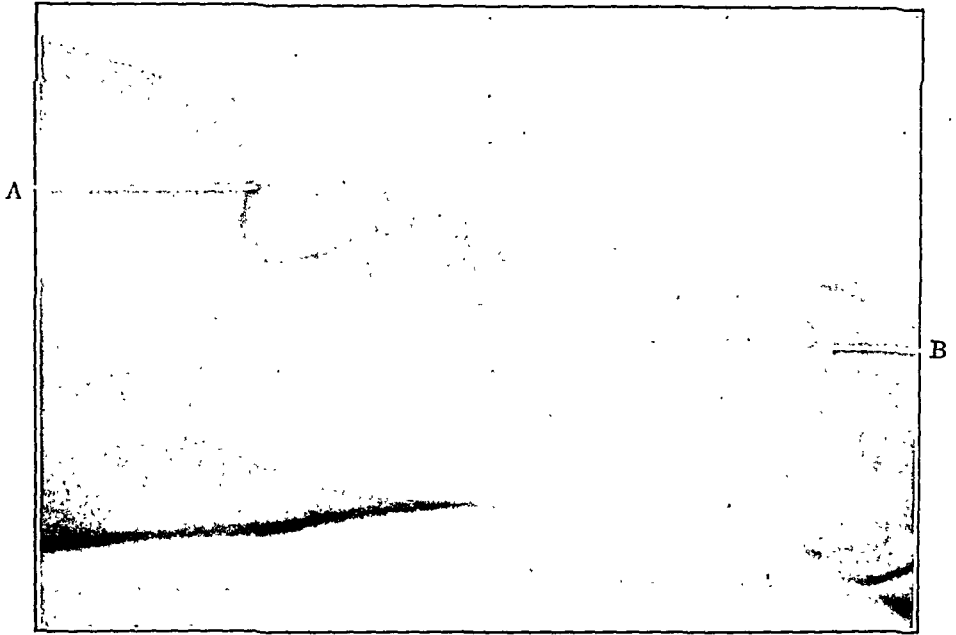


FIG. 3.—A, fully developed keloids; B, rudimentary papule-like forms.

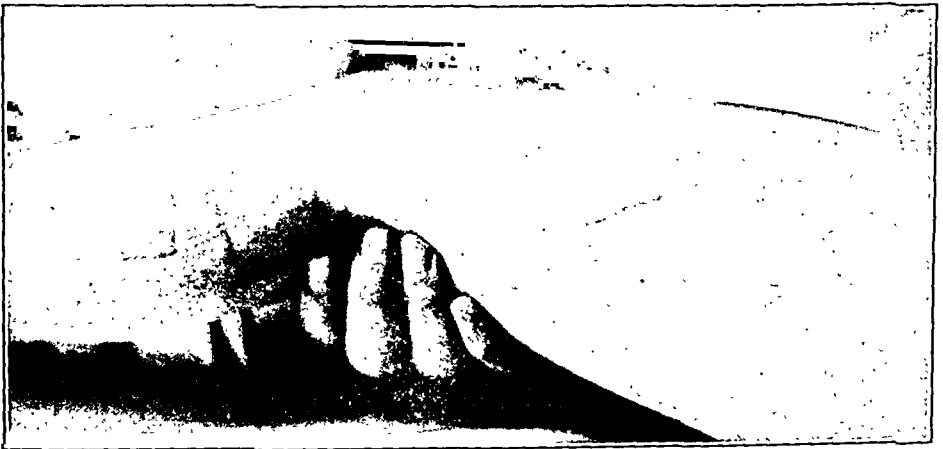


FIG. 4.—Linear scars surrounded by hyperpigmented areas. Residues of purpura on left leg.

straight line, about 4 cm. long, giving off three branches on both ends and in the middle, of about $\frac{1}{2}$ cm. each (Fig. 2 A). On the manifestation of the right lower leg it is more circular and horseshoe-like (Fig. 2 B). On all the lesions we find similar, more or less marked branches coming out from the chief line. On the smaller erythematous areas the scar formations are of rudimentary form, in the smallest areas being like papules (Fig. 3 B). The scar does not extend deeply into the skin, nor does it adhere to the subcutaneous tissue. They cause slight itching and, what the child describes as a pulling sensation.

Laboratory Findings: Blood: Leukocytes, 9900; hemoglobin, 80 per cent; red blood cells, 4,060,000; polymorphonuclears; 58 per cent; large lymphocytes, 7 per cent; small lymphocytes, 20 per cent; eosinophils, 14 per cent; basophils, 1 per cent; coagulation time, six minutes twenty seconds. Red cell fragility: Partial hemolysis at 0.35 per cent; complete at 0.2 per cent. The routine urine examination is negative, also for urobilin, urobilinogen and bilirubin. The stool shows no ova or parasites.

Course of Disease. August 8, 1924: The patient is being treated with fibrolysin injections (Merck), 1 ampule (1 cc) every third day. For the abdominal pain tinctura belladonnæ is being given. In addition, as a local application, pepsin hydrochlorid is used over two of the lesions (Unna,⁵ Wassermann⁶ and Friboes⁷).

September 2, 1924: The abdominal pains have disappeared. The erythema around the scars is fading. The scars, however, are still well marked but smaller in size; for instance, on the right upper leg 2 cm. long (against 4 cm. before). Most of the branches have completely gone. The eighth injection of fibrolysin is given. Pepsin hydrochlorid has been discontinued; since no difference in the appearance between the locally treated lesions and the untreated ones could be seen.

October 2, 1924: The child has had several bruises from fall on both legs which healed completely without formation of a scar. Fibrolysin has been discontinued after the fifteenth injection.

October 14, 1924: The von Pirquet test was done over the nevus, experimenti causa, in order to set a stimulus for a new scar. Blood count: Eosinophils, 8 per cent.

October 18, 1924: On the place of the von Pirquet scarification inside of the nevus two small depigmented areas are present. No scar or epidermal defect. von Pirquet was negative.

April 3, 1925: Examination of the child with special attention to skin was completely negative.

Comment. In summing up these data we have a case of keloid in a child who suffered a few months previously of acute purpura, of which residue was still visible. Some of the keloid lesions were observed while developing. The diagnosis keloid is definite, since

we have typical scar formation with the characteristic branches (Kele means "Claws of a Crayfish," Alibert⁸). In view of the well-developed scars no other dermatologic condition is to be considered in differential diagnosis. The purpura is apparently of the Henoch type, being associated with and followed by abdominal pains. The platelet count of 240,000 also points to the diagnosis of Henoch's disease, in which condition the platelets are usually not markedly diminished, but are normal or even increased (Lucas and Fleischer⁹). The purpura improved after tonsillectomy. The eosinophilia is to be noted while the skin eruption was present. An attempt to elicit keloid lesions artificially failed.

Mention is to be made of the increase in resistance of red cells to hypotonic salt solution, although the total count was normal. As animal experiments of Musser and Krumbhaar disclose, there is a decrease of the red cell resistance in artificial purpura.¹⁰ Should our observation indicate that during convalescence from purpura the resistance of the red cell increases possibly as a sign of the regenerative power of the organism? Unfortunately no further blood studies have been carried out.

On March 28, 1925, checking of the fragility showed: Hemolysis, partial at 0.35 per cent; total at 0.25 per cent; hemoglobin, 75 per cent; red blood cells, 3,720,000.

For treatment we intended to apply the most valuable measures—roentgen ray (Cumberbatch,¹¹ Pfahler¹² and Fox¹³), or radium (Daland,¹⁴ Harrison¹⁵) in case of failure of the fibrolysin treatment, which has been recommended by Gougerot.¹⁶ After fifteen injections of fibrolysin, however, the skin lesions disappeared completely and therefore the application of roentgen ray was unnecessary. Eight months after the treatment had been started the skin still appeared perfectly normal.

Discussion. The description of this case calls forth the following questions:

1. Does there exist a spontaneous protopathic keloid which arises on an apparently normal skin?

2. Is it possible that the hemorrhagic disease caused a disposition of the skin for keloid?

3. Are there any conclusions as to the pathogenesis of keloid suggested through the observation of the above described case?

Since Alibert's⁸ observation first has led to distinguishing two kinds of keloid, that is, one which develops from a skin area not the seat of a manifest injury and the ordinary keloid growing from a cicatricial change of the skin, there has been much discussion in the literature as to whether such a differentiation is justified. Warren, Kaposi¹⁷ and others tried to demonstrate histologic changes to uphold this division. Halbe, Hutchinson, Freund, Unna and, in recent years Heidingsfeld, disprove their arguments, and believe that careful histologic research brings to light features in both

groups which have been thought typical for either one of them. It seems to me that there are two factors which account for the divergence of opinion: (1) Many of the reported cases grouped under the diagnosis keloid are definitely something else, for example, molluscum fibrosum, neurofibroma, myofibroma, verrucca, lacking the characteristic bifurcated prolongations and the typical crests as postulated by Alibert; (2) the meaning of the words "true," "idiopathic" or "spontaneous" keloid is interpreted by different authors in different ways. Some use this term if the history fails to reveal a formerly existing scar (from an operation, burn and so forth). Some others apply it in another sense, referring to a preceding traumatism. It is evident that a classification on the latter basis cannot be upheld, since the occurrence of a trauma is as difficult to prove as to disprove. On the other hand, there are some cases of definite nonpostcicatrificial keloids described, for example, by Geyser,¹ McKee² and Heidingsfeld.³ The above case, in which some of the keloids were developing under our observation from skin lesions, which usually do not heal with scar formation, such as purpura hemorrhages and chickenpox, lends support to the old distinction of Alibert, at least from a clinical standpoint.

On careful search of the literature no case records could be found presenting an association of purpura with keloid. However, Minot and Lee¹⁸ do mention residue of purpura characterized by "elevation and induration beneath the skin, leaving a single bluish area usually 2 to 6 cm. in diameter, often with a raised lump in the central part." From this description one has to infer that these lesions are identical with the above described ones, with keloid.

The question arises: Might purpura be the cause of the keloid or at least have created a disposition of the skin to answer such a stimulus as mosquito bite or chickenpox papules by the peculiar production of keloid? This leads us to review the former theories on the pathogenesis of keloid. Most authors believe in a "general disposition" of the individual for keloid, usually not committing themselves in regard to the nature of this disposition. Alibert, Hebra and Hutchinson emphasize the hereditary factor. Justus¹⁹ concludes from the observation of 45 secondary keloid cases associated with some symptoms of hyperthyroidism that the glands of internal secretion, especially the thyroid, play a great part in the origin of this "keloid-disposition." He has even succeeded in producing keloid artificially in 12 of 15 hyperthyroid cases by such irritation of the skin as mustard plaster and carbon dioxide snow. Among the authors who deny the question of a general disposition, believing in a local agent on the seat of the keloid, are Balzar and Levy.²⁰ De Beurman and Gougerot²¹ hold that the tubercle bacillus can produce the lesion. Hyde²² publishes his observation on guinea pigs, which developed tuberculosis after injection of cell tissue excised from keloids.

In our dermatologic description we noticed that there was some residue of the former hemorrhages left in the form of some pigmented patches. It is well known that keloid is observed chiefly in negroes, in whom we see a natural hyperpigmentation. Furthermore, displacement of pigment has been found as being associated with keloid by former investigators. Welander²³ tattooed a white man with certain dyes. With some he produced keloid, whereas other ones, like the ordinary blue tattoo dye, were without any effect on the skin. In addition, there is no doubt that the production of all scars goes hand in hand with a certain displacement of the skin pigment. We, therefore, have enough evidence to justify the opinion that in our case the change in the pigment distribution, brought about by purpura, may account for the existence of keloid. Moreover, we recall that the child had a large nevus pigmentation over the scapular region. Although we were unable to produce keloid over this area by scarification, I wish to make mention of the possible relationship of this nevus to the genesis of the keloid. Also the other peculiarities of the patient's skin, such as the slow tendency of the mosquito bites to heal and the marked edema of the foot around the mosquito bite lesion, should be mentioned.

With this in mind, especially considering that all scars are associated with displacement of pigment, we see that the question of idiopathic or false keloid assumes another aspect. Instead of the old debate, is there a scar or no scar as a preëxisting causative agent, it might be useful for further investigators to inquire whether there is a change of the pigment distribution as the underlying cause for the keloid, either in the présence or the absence of a scar. This consideration would naturally not lead us much nearer to the solution of the keloid problem, but it might be a step forward on the difficult path leading into the still unexplored large provinces of the pathology of the tumor and of the pigmentation.

Summary. 1. A case of multiple keloid is described which did not arise from a preëxisting scar. Some of the lesions developed under observation.

2. There were definite changes of the pigment distribution of the skin following Henoch's purpura, from which the child had suffered five months previously. There was also a nevus pigmentosus present. The skin had a tendency to heal slowly after mosquito bites.

3. The patient's blood picture showed definite eosinophilia while the keloid was present.

4. The lesion healed after fibrolysin injections. Pepsin hydrochlorid compresses, locally applied, were of no evident value.

5. The opinion is expressed that the presence of pigment disturbances of the skin might be a useful guide in further studies of the Keloid problem, and might help to eliminate further controversy on the question of idiopathic and secondary keloid, in view of the fact

that all scars cause some displacement of the normal pigment conditions of the skin.

(I wish to thank Dr. Udo J. Wile, Ann Arbor, for suggestions given in reviewing this paper.)

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SUBPHRENIC ABSCESS: A CLINICAL STUDY.*

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LOCALIZED suppuration beneath and in more or less intimate contact with the diaphragm, usually termed subphrenic or sub-

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diaphragmatic abscess, offers to the medical man or surgeon a most difficult diagnostic problem. Mistakes are frequent and often justifiable. Insidious in onset, protean in its manifestations, this condition may present a symptomatology so varied and so misleading that definite diagnosis is at times impossible and can only be made with certainty by operation or at autopsy. Let us consider briefly a history such as the following:

Case Reports. CASE I.—Mrs. E. S., a young woman, aged twenty-six years, was admitted to the surgical wards of the Mount Sinai Hospital, December 28, 1922, with the usual signs and symptoms of acute appendicitis. At operation a badly inflamed, almost gangrenous, but not ruptured appendix was removed and the wound closed without drainage. An uneventful postoperative recovery followed and the patient was discharged in twelve days apparently well.

Two months later she was readmitted to the medical wards, complaining that for several days she had been having attacks of chills, fevers and sweats lasting often for two hours and accompanied by vomiting. She complained also of pain in left lower chest and a cough with scanty expectoration. This history together with physical findings of dulness and absent breath sounds at left base suggested a lung or pleural lesion. A roentgen ray of the chest, however, showed no evidence of consolidation or effusion and both diaphragms were normal in position and regular in outline. A negative Widal reaction, sterile blood culture and the presence of leukocytosis seemed to exclude a possible typhoid infection and failure to find malarial parasites in smears ruled out malaria. Because of the septic temperature, the history of a previous appendectomy and the marked tenderness on pressure over the lower chest and splenic area, a tentative diagnosis of abscess of the spleen or subphrenic area, was made. Operation, performed March 24, 1923, revealed a large mass in the left hypochondrium which seemed to be the spleen enlarged to six times its normal size, apparently the seat of multiple infarcts. No subphrenic collection could at this time be made out. Puncture of the spleen with a needle detected no pus and the wound was closed without drainage. The postoperative course was stormy, patient grew progressively worse, temperature increased and, in spite of transfusion, death resulted nine days after operation.

Autopsy revealed a huge subphrenic collection of pus which was situated behind the spleen pushing it forward and thus accounting apparently for the fact that it was not discovered at operation, but simply considered part of a large spleen. The spleen at autopsy was just a trifle larger than normal and contained many degenerated cysts.

In this case in a consideration of its differential diagnosis condi-

tions so seemingly varied as typhoid fever, malaria, pleurisy with effusion, lung abscess and abscess of kidney or spleen had to be ruled out and even then, in spite of roentgen-ray examination and operation, diagnosis could only be made with certainty at autopsy. Similar and more recent cases have served to emphasize the diagnostic difficulties of this condition.

In an effort to bring before our minds a clearer picture of subphrenic abscess a clinical study of some of our cases gathered from our records together with additional facts gleaned from recent literature on this subject seemed worthy of presentation.

Since 1921 only 6 cases have been seen in our medical and surgical wards, indicating how infrequently this condition occurs.

In order to appreciate more clearly the location and causes of these abscesses and from the standpoint of operation in order to determine the best method of approach for drainage, some knowledge of the anatomy of the subphrenic spaces is necessary. Detailed description of these spaces particularly of their divisions into the six areas, as given originally by Barnard,¹ will not be attempted. For practical purposes it is only necessary to remember that the subphrenic spaces lie in the upper portion of the abdominal cavity beneath the under surface of the diaphragm in the so-called supra-colic area and that in this area they are subdivided into the right and left subphrenic spaces by the falciform ligament of the liver. The right subphrenic space is therefore in relationship anatomically above with the right portion of the diaphragm, while below it is in relationship with the liver and posteriorly with the gall bladder, duodenum and upper pole of the right kidney. Abscesses in this space usually originate from lesions of these organs such as abscesses of the liver or kidney; duodenal ulcer or infection of the gall bladder or ducts. The right space connects freely with other fossæ and particularly by way of the right lumbar groove lying between the ascending colon and loin with the appendiceal and pelvic regions. As a consequence appendicitis is a common etiologic factor and most of the abscesses caused by it are right sided, although left-sided abscesses do occur, as in the case already cited.

On the other hand, the left subphrenic space situated beneath the left portion of the diaphragm is in relation with the many organs: the spleen, left lobe of the liver, cardiac end and posterior wall of the stomach, left kidney and adrenal and tail of the pancreas. Lesions of these organs, therefore, may by perforation or extension result in abscesses of this space—often called perigastric or perisplenic and because of the many conditions in this region which they may simulate it is little wonder that the differential diagnosis is so difficult.

It is natural for anatomic reasons that the location of these abscesses should depend in large measure upon the causes and that among the most common of these, appendicitis, ruptured peptic

ulcer and infections of the liver or gall bladder should predominate. Unquestionably gravity plays a great part in the selection of the subphrenic space for localization of the abscesses; thus, if for any reason fluid accumulates in the peritoneal cavity either before or after operation and the patient is not in a sitting posture, this fluid will tend to gravitate to the subphrenic spaces instead of flowing down over the lumbar elevations into the pelvis. Here absorption is not so rapid, abscesses not so prone to develop, and even if they do, they can be more easily dealt with, particularly in the female. It is a peculiar fact in this connection that most subphrenic abscesses occur in males (84 out of 113 in Mayo series).² This is no doubt best explained by the fact that anatomic variations between the male and female pelves allow the lumbar grooves to drain more readily into the pelvis of the female than of the male and therefore in the female, pelvis abscess is more commonly the sequel than subphrenic abscess. Extension of intrathoracic suppuration through the diaphragm to cause a subphrenic abscess is indeed a rare occurrence and is best explained by the fact that the current of lymph flow through the diaphragm is ascending and not descending. Focal infection is also mentioned in the literature as an etiologic factor, and though cases have been cited as apparently due to carbuncles, cellulitis or dental infection, this mode of infection is the exception rather than the rule. In most cases, the abscess is due to infection from some abdominal viscus.

Acute appendicitis, particularly the type which is neglected and allowed to go several days or weeks before operation, is far too frequent a cause of subphrenic abscess. In this type one obtains a history similar to the following:

CASE II.—M. S., a boy, aged seventeen years, was admitted to the Mount Sinai Hospital August 31, 1921, with pain in the right iliac fossa of three weeks' duration, septic temperature, leukocytosis, marked tenderness and rigidity over the hypochondrium with only slight tenderness over McBurney's point. At first the diagnosis of cholecystitis or high-lying retrocecal appendicitis seemed likely. On account of some vague signs in the lower chest posteriorly, a roentgen ray of the chest was taken and revealed no lung lesions, but did show elevation of the right diaphragm with no irregularity in outline. The diagnosis of subphrenic abscess was then made and verified at operation. The abscess was drained and a large subacutely inflamed appendix removed. After a rather stormy convalescence, lasting over six weeks, the patient left the hospital with a moderate anemia and a small discharging sinus which required considerable time to heal.

In this case an earlier recognition and prompt operation would have prevented the formation of the abscess, shortened materially the convalescence and promoted the well-being of the patient.

More often, however, the abscess forms after the appendectomy has been done. Thus Ross³ reports an incidence of about 0.8 per cent in a series of over 3300 appendectomies at the Lankenau Clinic. It is more apt to occur in a highly placed, retrocecal, gangrenous appendix, where ascending retroperitoneal infection is already present at the time of operation. This method of spread of infection (namely, through the retroperitoneal cellular tissue) is the most common. Infection can, however, be carried through the lymph channels or rarely through the portal or general circulation. In this type of case, the symptoms appear several days after operation, as in the following case:

CASE III.—A. L., a man, aged twenty-five years, was admitted to the Mount Sinai Hospital, September 3, 1921, complaining of pain in the lower right abdomen and vomiting for five days with a history of similar previous attacks. His temperature and pulse were normal, lungs presented no abnormal signs, and there was but slight tenderness and rigidity at McBurney's point, with only a slight leukocytosis. At operation, performed the day of admission, an acutely inflamed appendix was removed and the wound closed without drainage. Following the operation, the patient did poorly. He complained of pain in the incision and the right lower chest and back and had a variable but high temperature. A week following the operation considerable pus was evacuated from the incision with but slight relief to the patient. Examination several days later revealed decreased fremitus with dullness and absent breath sounds at the right base and also a leukocytosis of 14,000 with 93 per cent polymorphonuclears. Roentgen-ray examination at this time showed a dense shadow over the lower right pulmonary region with displacement of the heart to the left, suggesting pleural effusion, although a subdiaphragmatic collection could not be excluded. The patient grew steadily worse, began to have chills and looked septic. On October 7, more than a month after the first operation, a longitudinal incision was made into the right loin below the ribs and considerable pus evacuated from a pocket behind the kidneys. Following this operation the patient gradually improved, his temperature gradually returned to normal and after a convalescence lasting over two months, he was finally discharged in good condition January 3, 1922. Roentgen-ray examinations made subsequent to the second operation showed gradual but progressive improvement in the pulmonary involvement with the diaphragm elevated, immobile and slightly irregular in its outer portion, no doubt due to an existing pleuritis.

In this case symptoms of subphrenic involvement began to show themselves four days after operation and continued for almost a month before the abscess pointed in the loin. Of particular interest in this case are the chest symptoms and signs. These are present

in almost every case, and offer one of the greatest obstacles in differential diagnosis. Because of the comparative frequency of post-operative lung complications, especially pneumonia, it is quite natural for any lung signs or symptoms occurring after operation to be mistaken for a pulmonary complication and lead to a delay in the recognition of the true underlying cause. This is well exemplified in Case IV.

CASE IV.—J. D. S., a boy, aged fifteen years, was admitted to the Mount Sinai Hospital April 27, 1923, with the usual symptoms and signs of acute appendicitis of two days' duration. At operation a suppurative appendicitis was found which was removed and drainage-inserted. His condition immediately following operation seemed fairly good. At the end of three days his temperature was normal and the wound seemed to be draining fairly well. On the fourth day, however, the patient began to have a slight cough and an expectoration, the temperature increased and on account of the symptoms together with a polymorphonuclear leukocytosis and physical signs at the right base suggestive of consolidation (dulness and tubular breathing) pneumonia was considered. Roentgen-ray examination at this time showed evidence of pleurisy with a slight effusion and an incomplete consolidation involving the lower portions of the right lung. The outlines of the diaphragm were completely obliterated, making it impossible to distinguish between a subdiaphragmatic and a supradiaphragmatic collection (Fig. 1). With improvement in the wound drainage the patient gradually became better, his temperature fell and the cough decreased in intensity. Physical signs at the base persisted for some time, but chest roentgen-rays taken subsequently showed gradual absorption of the effusion and improvement in the lung picture. With absorption of the fluid, the right diaphragm was then seen to be somewhat elevated, indicating that a subdiaphragmatic collection had been present. The patient was discharged June 3, 1923, apparently well, in spite of roentgen-ray evidence of slight basal involvement. Follow-up showed no return of any symptoms during the following year.

In this case the presence of the subphrenic abscess was further complicated by pleurisy with slight effusion and inflammatory involvement of the lower lung, no doubt the result of upward extension of the subphrenic infection through the diaphragm. The complication is a fairly frequent one, and is one of the prime obstacles in making a diagnosis of abscess possible. In this type of case, history is most important, since roentgen-ray findings lend no assistance.

From a review of the cases already cited it can be readily seen that the symptomology is varied and dependent largely upon the

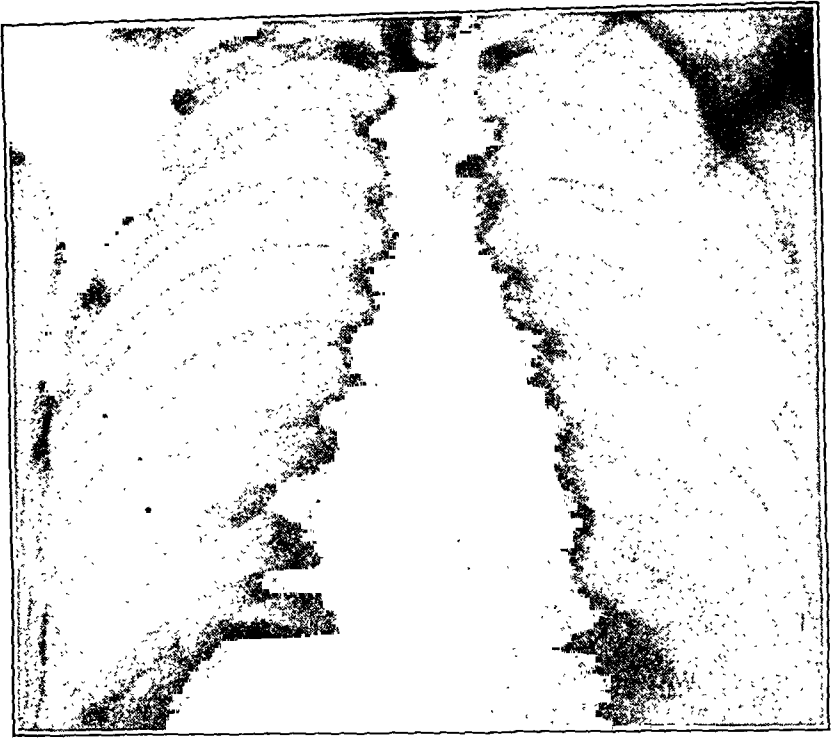


FIG. 1.—Case IV. Chest roentgen ray indicating difficulty of making diagnosis by roentgen ray when subphrenic abscess is complicated by pleural effusion.

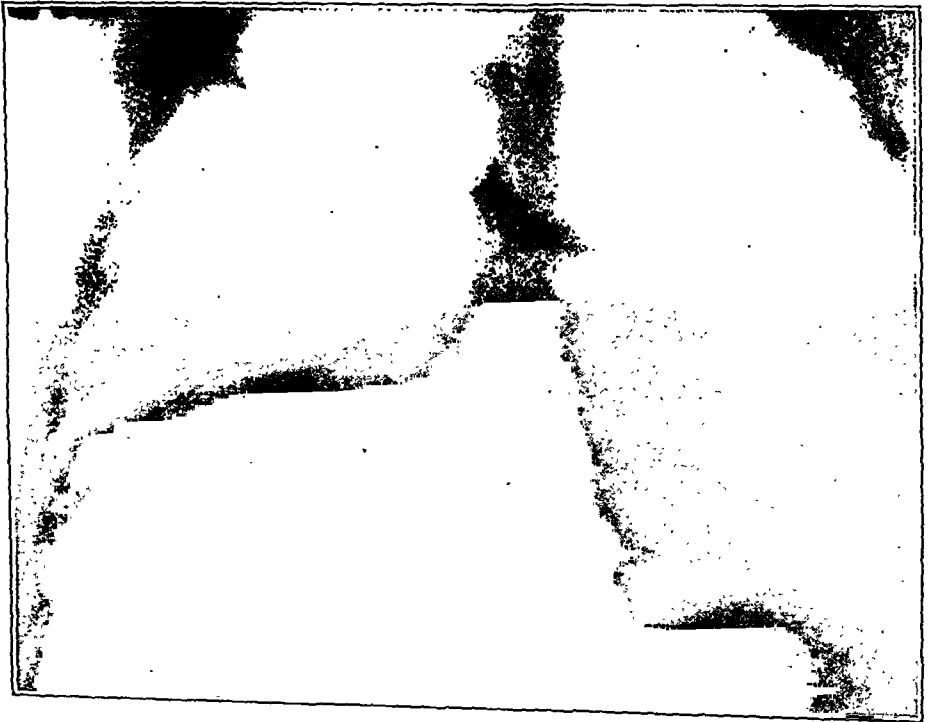


FIG. 2.—Case VI. Chest roentgen ray showing elevation of diaphragm due to subphrenic collection.

etiology, location, and more particularly upon the character of the onset—when acute, as in ruptured ulcer, the onset is usually abrupt with acute abdominal pain and vomiting of either bloody or bilious material followed later by constitutional signs of suppuration, namely, fever, rapid pulse, chills, sweats, pallor and a polynuclear leukocytosis. More often, however, the onset is insidious, and in these types the most constant symptoms are: (1) Pain at the costal margin referred to the back or shoulder. (2) A church-steeple type of temperature curve, that is, one showing marked variations with corresponding increase in the pulse rate, but rarely in the respiratory rate. This lack of correspondence between the respiratory and the temperature-pulse curve, when associated with a chill and leukocytosis is very diagnostic of inflammation about the diaphragm. (3) Leukocytosis. This serves to indicate the presence of suppuration, but not its location. (4) A short diaphragmatic cough present in many cases particularly when there is coexistent pleural involvement. Severe cough with marked expectoration occurs only after rupture of the abscess into the lung.

Physical signs are as variable as the symptoms; in fact, in the early stages no local signs may be found unless carefully looked for. One of the early signs is a limited excursion of the diaphragm on the affected side, also a retraction of the interspaces directly over the abscess. In right-sided abscesses not containing gas, the area of liver dulness is increased and often friction sounds are heard over the dome of the liver, indicating basal intrathoracic involvement. As the abscess gets larger, signs of lung compression begin to appear and the area of liver dulness increases. When this occurs, there is usually bulging of the lower ribs or a mass in the lower abdomen on one side, with deep-seated tenderness on pressure. If the abscess contains air, the diaphragm may be pushed up to the level of the second or third rib, giving physical signs on percussion and auscultation of a pneumothorax particularly the tympanitic resonance and movable dulness—this form has been called pyopneumothorax subphrenicus.

At best, physical signs offer but little assistance in diagnosis, particularly in the early stages. Probably the most valuable single diagnostic aid, aside from history is the roentgen ray and fluoroscope. Use of the latter is often prevented by the patient's condition. It should, however, be used whenever possible, as it gives valuable information hard to elicit by other methods. A dome-like elevation of the diaphragm into the thorax with a limitation of the diaphragmatic excursion on breathing and an acute costophrenic angle in the absence of lung involvement is almost pathognomonic of subphrenic abscess (Fig. 2). Where, however, the abscess is complicated by pleural effusion or empyema on the same side, it is impossible to separate the shadows and diagnosis must be made by other methods (Fig. 1). A point of value in differentiating

abscess from pleural effusion, is the fact that in abscess, the heart is seldom displaced laterally, although it may be pushed up. In gas containing abscesses, a pocket of air lying beneath the diaphragm will show on the plate and if the patient can be fluoroscoped either in a standing or in a lateral position, lying on his unaffected side, then a distinct fluid level, lying below the gas, can be made out.

Exploratory puncture of the posterior chest for diagnosis is somewhat dangerous and should only be used when absolutely necessary or to rule out pleural effusion. It should always be carried out in the operating room where preparation for an immediate incision and drainage has been made, should the abscess be located. In the latter instance, to prevent infection of the pleural cavity, the needle should be left *in situ* and incision made down upon it immediately. A negative puncture does not rule out the possible presence of an abscess.

In the final analysis the diagnosis of subphrenic abscess is dependent on the history, mode of onset, physical signs and roentgen-ray findings, and even in spite of these the abscess is frequently overlooked. It is easy enough to diagnose suppuration in these cases; but to locate its site, is a problem sometimes impossible of solution. At times, in spite of history and other diagnostic aids, the abscess is overlooked entirely and not discovered except at autopsy, as occurred in the following case:

CASE V.—Mr. M. N., aged forty-nine years, was admitted to the Mount Sinai Hospital, November 8, 1924, with pain in the right hypochondrium and vomiting but no fever or jaundice. There was a history of frequent attacks of right upper abdominal pain and indigestion for a number of years but the present attack dated back three weeks. Examination showed exquisite tenderness and slight rigidity in upper right abdomen with a distinctly palpable liver edge. The temperature and pulse were normal and there was a leukocytosis of 13,800 with 72 per cent polymorphonuclear. Operation performed the day of admission under local anesthesia revealed an acutely inflamed greatly thickened gall bladder filled with calculi and surrounded with extensive adhesions to the duodenum and transverse colon that were separated with considerable difficulty. A cholecystectomy and appendectomy was done and drainage of the gall bladder fossa was inserted. The wound drained but slightly and after a few days the tube was removed leaving a small sinus from which some pus discharged itself. Except for some discomfort in the right upper abdomen and slight vomiting, the patient appeared to improve, temperature and pulse being at this time normal. Twenty days after operation there was a sudden rise of temperature to 104° with rapid pulse, difficulty in breathing and vomiting. Physical signs at the right base, dullness and distant breath sounds, suggested

a pulmonary complication. In the course of the next few days the temperature dropped, the pulse improved, and the patient appeared on the way to recovery. On December 5, four weeks after operation, the patient suddenly became worse, with feeble pulse; and in spite of stimulation, death ensued. At autopsy the gall bladder fossa was found to be perfectly clear. A large subphrenic abscess was found situated in the anterior portion of the right subphrenic space, which accounted for the patient's death.

It is very probable that the abscess in this case formed postoperatively since symptoms did not show themselves for almost three weeks and as a rule, it takes but two weeks for the abscess fully to form itself. Here again, the pulmonary symptoms and signs aided in overlooking the presence of the abscess. This is not infrequent, however, in the Mayo Series, 27 of the 117 cases reported came to autopsy undiagnosed, and many of these were overlooked at operation.

Though subphrenic abscess may resemble many other conditions, the problem of differential diagnosis, practically resolves itself into distinguishing between hepatic abscess, pleurisy with effusion, particularly empyema. History, physical signs and roentgen-ray findings in these two conditions will usually serve to distinguish them. Thus in pleural effusion, there is often a history of previous pulmonary infection, the heart is shifted laterally, the area of dulness changes with the position of the patient and roentgen ray shows a flattening of the dome of the diaphragm instead of an elevation. In hepatic abscess, particularly the parasitic form, there is often a history of diarrhea, the area of liver dulness is not only enlarged upward but also downward (a thing which is unusual in subphrenic abscess) and finally the diaphragm though elevated in the roentgen-ray plate is usually irregular in outline.

If these conditions were to occur singly, diagnosis would not be difficult but more often they occur together. This is especially true in the case of hepatic abscess which often ruptures into the subphrenic space and thence involves the pleural cavity as occurred in Case VI.

CASE VI.—B. G., a boy, aged nineteen years, was first admitted to the Mount Sinai Hospital, December 7, 1923, complaining of pain in the right lower chest, slight fever, occasional attacks of diarrhea and weakness, these symptoms being of about three months' duration. He was born in southern Russia and came to this country only a few months prior to admission. Several weeks previously he had been in another hospital for the same complaints and a diagnosis of pleurisy had been made. Examination showed diminished fremitus and breath sounds with impairment of resonance at the right base and a tentative diagnosis of pleurisy was made.

At the end of three weeks he left the hospital but slightly improved.

After his discharge, the pain recurred and the weakness became so marked, that for two weeks prior to his readmission he had to remain in bed. He was readmitted January 30, 1924, with the same symptoms. Examination at this time showed an increased area of flatness with absent breath sounds at the right base, a distinctly palpable liver edge, temperature of 101° and a slight leukocytosis. Roentgen-ray showed a dense shadow on the right side with elevation of the diaphragm, apparently due to a subphrenic collection (Fig. 2). There was also slight displacement of the heart to the left. On February 2, a resection of the eighth and ninth ribs posteriorly was done, revealing a subphrenic collection arising from a large hepatic abscess. This was incised and drainage tubes inserted. Examination of the pus from the abscess revealed the presence of ameba. The postoperative course was stormy, there was evidence of an increasing pleural effusion and the patient grew progressively worse until the time of his death February 17. Postmortem examination showed a large subphrenic abscess and a plastic pleurisy with moderate effusion. The lower portion of the right lung also showed evidence of inflammatory changes.

This case well illustrates the delay in diagnosis caused by the presence of pleural complications. With earlier diagnosis and prompt treatment a fatal outcome might have been prevented. In reviewing the causes of death of 36 fatal cases in his series, Barnard found that in 24 of these, death was avoidable, in 50 per cent by earlier recognition, and in the other 50 per cent, by better drainage at operation. Without operative measures, the outcome is almost certain to be fatal, death occurring either by septicemia or by rupture into the lung, pericardium, stomach, or less often into the bowel. It is possible for the abscess to burrow into the skin and evacuate itself spontaneously, but this occurrence is exceedingly rare. Even with operative treatment, the prognosis in these cases is not very hopeful, mortality being from 20 to 40 per cent in most of the clinics. It is dependent in large measure upon the cause—thus in abscesses due to ruptured peptic ulcer, it is apt to be higher than in those of appendiceal origin.

The treatment of these abscesses, as with any abscess is strictly surgical, consisting of incision and complete drainage. The method of approach to the abscess is best decided upon by the surgeon and is determined largely by the location of the abscess and condition of the patient. A thorough knowledge of the anatomy of the subphrenic spaces will aid greatly in deciding the type of operation to be done. Three methods of approach are generally used: (1) A lumbar incision—if the abscess points here; (2) abdominal incision; (3) through the chest wall posteriorly. In this method the incision is made either below the pleura or through it. In either case the pleural cavity should be protected from infection before opening

the diaphragm. As a rule the posterior method is the method of choice as it insures more complete drainage. Any method which insures easy access to the abscess and complete drainage will be the best for the patient for it is upon this that the outcome depends. Careful study of autopsy findings in the fatal case of Barnard's series upon which operation had been done showed very distinctly that the death was usually due to incomplete drainage as a result of insufficient exposure of the abscess.

Conclusions. From these observations the following conclusions may be drawn: 1. Subphrenic abscess, though infrequent, is a serious condition and often fatal. Convalescence from it is long, tedious and sometimes attended by a thoracic or renal complication that may make the patient a chronic invalid.

2. The location of the abscess is dependent in large measure upon the cause. In the selection of space, gravity plays a large role. Efforts should therefore be made to prevent this by the use of the Fowler position postoperatively.

3. Subphrenic abscess is always secondary to infection elsewhere; most often from a neighboring abdominal focus.

4. Since the majority occur postoperatively, abscess should be suspected in all patients who for no obvious reason maintain a variable type of temperature-pulse curve.

5. Diagnosis is made chiefly upon the history, mode of onset and physical signs. Roentgen ray and fluoroscopy, particularly the latter, are often invaluable diagnostic aids except in the presence of thoracic complications.

6. The frequent occurrence of thoracic complications adds greatly to the difficulties of differential diagnosis.

7. Needling of the thorax should only be performed when absolutely necessary. It should always be done on the operating table under anesthesia with full preparations for immediate operation.

8. Early diagnosis followed by prompt incision with complete exposure and thorough drainage of the abscess will do much in producing a favorable outcome. A thorough knowledge of the anatomy of the subphrenic spaces is essential in determining the best methods of approach to the abscess.

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REVIEWS.

RHEUMATIC HEART DISEASE. By CAREY F. COOMBS, M.D., F.R.C.P. (LOND.). Pp. 376; 51 illustrations. New York: William Wood & Co., 1924. Price, \$4.50.

IN his preface the author points out the fact that rheumatic heart disease has not hitherto been made the subject of a monograph. This deficiency in the literature has here been most completely and satisfactorily supplied. Etiology, morbid anatomy and histology, morbid physiology, as well as the symptomatology, diagnosis, prognosis, treatment and prevention are discussed. The book will be found invaluable by the elementary student. Clinicians of experience will be interested in the chapters on physical signs, course and prognosis, since their subject matter is based on the author's extensive observations. The studies on the course of the disease constitute a very important contribution.

C. W.

THE ACTION AND USES IN MEDICINE OF DIGITALIS AND ITS ALLIES. By ARTHUR R. CUSHNY, M.A., M.D., LL.D., F.R.S., Professor of Pharmacology in the University of Edinburgh. Pp. 303; 77 illustrations. Longmans, Green & Co., 1925.

THOSE who are acquainted with Cushny's *Pharmacology* and his monograph on "The Secretion of the Urine," are well aware of his breadth of view, clarity of expression and ability in critical analysis. His new book, on a subject in which he has been particularly interested for many years, and on which a great amount of work has come from his laboratory, is of the same high standard as the others. The writer has long been recognized as the outstanding authority on digitalis, and this book, therefore, may be considered the most authoritative account that can be written at the present time.

The book is most comprehensive in its contents and scope. It begins with an historical account of the use of the digitalis group in medicine. The second chapter deals with the chemistry of the group, and the present state of knowledge of this confusing subject is clearly stated. The basic principles of digitalis action are

described in detail in a chapter on its action on the frog's heart, and from this the author passes to the action on the mammalian heart, a subject on which he is particularly well versed through his own work. This pharmacologic section might well serve as a model for orderly sequence, completeness and clearness in presentation.

The use of digitalis in therapeutics is discussed at length. The author's collaboration with Mackenzie has given him a first-hand knowledge of digitalis therapy, and the chapter on this phase of the subject, dealing with the mechanism of digitalis action in the various forms of cardiac disease, is of great practical interest. The book ends with a chapter on administration and a critical analysis of current methods of assay. The extensive bibliography given, which includes practically all the important contributions to the subject, will be invaluable to workers in this field. An engraving from a portrait of William Withering serves as a frontispiece. The illustrations are abundant and unusually well done.

The book is remarkable in the well-rounded and even way in which all sides of the subject are presented. It will be read with the greatest profit by all students of medicine and particularly by those who are working on cardiac disease.

G. W.

NEUERE ARZNEIMITTEL: IHRE ZUSAMMENSETZUNG, WIRKUNG UND ANWENDUNG. By PROF. DR. MED. C. BACHEM, Instructor in Pharmacology, University of Bonn. Third edition. Pp. 141. Volume 669 of the Götschen Collection. Berlin and Leipzig: Walter de Gruyter & Co., 1925.

THIS little volume states briefly the composition, action and therapeutic use of a large number of therapeutic agents that have been put on the market during the past fifteen years. Particularly in Europe has there been a flood of such drugs, usually under trade names, and many of them have found a vogue and fill a useful place in medical practice. For the most part only drugs that have shown themselves to be of practical value have been included in the book. It is unfortunate, however, that the author was not a little more critical in some instances: for example, an insulin preparation for oral administration.

R. K.

CLINICAL FEATURES OF HEART DISEASE. By LEROY CRUMMER, M.D., Professor of Medicine, University of Nebraska. Pp. 353. New York: Paul B. Hoeber, Inc., 1925.

THE author's discussion is limited almost exclusively to the purely clinical aspects of heart disease. Nearly one-fourth of the book is

devoted to history-taking, inspection, palpation, percussion and auscultation, and only twelve pages to mechanical aids in diagnosis. The style is extremely attractive, clear and easy to read, and the subject-matter is presented in an interesting, even fascinating manner. It is all the more regrettable therefore that the book has serious faults requiring mention. Many statements are made in an unjustifiably categorical manner. Opinion is sometimes presented as though it were established fact. Far too many misstatements are found, such as the following: "Paroxysmal tachycardia, flutter and profound fibrillation are quite unknown in aortic insufficiency." It is of course well known that auricular fibrillation is not infrequently found in hearts with aortic insufficiency, with or without associated mitral valvulitis.

The book will be read by experienced students of heart disease with interest, pleasure and profit, but it does not distinguish sharply enough between opinion and established fact to be unreservedly recommended for the beginner.

C. W.

MEDICAMENTS ET MEDICATIONS CARDIAQUES. By H. VAQUEZ, Professeur a la Faculté de Médecine de Paris. Lectures collected by M. Theodorescu. Pp. 302. Paris: J. B. Baillière et Fils, 1925.

THE author states that these lectures were primarily designed for the instruction of the assistants in his service. At the request of M. Theodorescu he consented to have them written and published. The drugs employed in heart disease are adequately discussed, as is the hygiene of the cardiac. The latter half of the book is devoted to the treatment of the various clinical manifestations of heart disease. The arrangement of the lectures makes information desired on any subject readily accessible. The book easily ranks as one of the best on the treatment of heart disease. It is to be hoped that an English translation will be made.

C. W.

AN INTRODUCTION TO SEXUAL PHYSIOLOGY. By F. H. MARSHALL, F.R.S. Pp. 167; 72 illustrations. London: Longmans, Green & Co., 1925.

BEGINNING with the methods of reproduction in the lower animal forms and progressing to similar functions in the mammals, this book considers the physiology of reproduction in a satisfactory manner. Chapters on Heredity, Fertility and the Internal Secretions enhance the value of the volume, and it should be of assistance to students of medicine and biology, more particularly the latter.

F. B.

A SYNOPSIS OF GYNECOLOGY. By ARTHUR GRAY, F.R.C.S., M.R.C.P., Gynecological Surgeon, Hampstead General Hospital. Pp. 352; 7 illustrations. London: Edward Arnold & Co., 1925.

THIS book is not designed to be a general textbook, but is written in the form of a syllabus. The material is based on the author's lecture notes and is so condensed into important headings and sub-headings, with brief but valuable comments, that it is ideally suited for students preparing for examinations as well as for instructors who wish to quickly review the subject. A little too much attention is paid to endometritis which is now admittedly a rare condition. The author apparently has not been won over to the use of radium in cancer of the cervix, as he advises operation in all but advanced cases.

F. B.

DISEASES OF THE EAR, NOSE AND THROAT. By HAROLD HAYS, M.A., M.D., F.A.C.S., City and Riverside Hospitals, New York City. Pp. 969; 550 illustrations. Philadelphia: F. A. Davis Company, 1925.

THE author has prepared this work especially for the use of the student and general practitioner. The problems of otolaryngology are admirably presented in a clear and commonsense manner. Of particular merit is his chapter on Progressive Deafness, in which he emphasizes the importance of careful supervision and treatment of the partially deaf child. Not only will the student and practitioner be benefited by the information this book contains but the internist, pediatrician and otolaryngologist will do well to give it their attention.

K. H.

HEREDITARY DISORDERS OF BONE DEVELOPMENT (PART I). By PERCY STOCKS, M.D., D.P.H., with the assistance of AMY BARRINGTON. Pp. 182; 16 plates. London: Cambridge University Press, 1925.

THIS is one of the memoir series from the Francis Galton Laboratory for National Eugenics, and is Volume III of *The Treasury of Human Inheritance*. The disorders of bone development showing tendency to hereditary transmission dealt with are multiple exostoses (diaphysial aclasis), multiple enchondromata, cleidocranial dysostosis, congenital dislocation of the radius and rare conditions designated "la pléonostéose familiale" and "hereditary osteitis."

The data is treated statistically, with emphasis on hereditary

influences. Pedigrees of 210 families are diagrammatically represented. The main anatomic and pathologic features are illustrated in nine plates, supplemented by brief descriptions of normal bone development and the pathology of the conditions treated.

A bibliography of 1050 titles is reviewed. Karl Pearson, in the introductory note, asks for more subscribers to the series. Volume II of the *Treasury* deals with hereditary diseases of the eye, and is partly published. R. A.

STATISTICAL METHODS FOR RESEARCH WORKERS. By R. A. FISHER, M.A., Fellow of Gonville and Caius College, Cambridge; Chief Statistician, Rothamsted Experiment Station. Pp. 239; 10 graphs; 67 tables. Edinburgh and London: Oliver & Boyd, 1925.

BIOLOGIC research is characterized, as a rule, by smaller groups of observations than those usually submitted to statistical analysis. This has stimulated the preparation of this book, which stresses particularly the statistical methods applicable to biologic problems. No one unfamiliar with the technic and terminology of statistical methods will be able to follow the full sense of the text without arduous study of its pages. However, a merit of the book is the wealth of examples illustrating the application of the various methods to particular biologic problems and from these examples some appreciation of the place of these methods in biologic research may be easily obtained. J. A.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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A Clinical Classification of Bright's Disease.—The varied classifications of Bright's disease offer one of the difficulties to the proper understanding of the disorder which presents itself to students, and clinicians as well. Until there is a well-comprehended, thoroughly established nosology of the several types of kidney disease the study of the disorders of this organ will not be on the same high plane as the studies of the heart, for example, or of the infectious diseases. If the student cannot understand just what an author means or what his language implies exactly confusion is bound to be present. The trouble in recent years has been that the internist is dissatisfied with the anatomical diagnosis made by the pathologist because, as THOMAS ADDIS (*Jour. Am. Med. Assn.*, 1925, 85, 163) writes, his observation is limited to one moment of time and that moment the last of life. To obviate the discrepancies between the clinical picture of Bright's disease and the pathologic findings resource has been had to the so-called functional diagnoses. Pathologists may differ in their conception of the microscopic lesions, but how much more do clinicians differ when they attempt a classification of the protean disease upon any one of a number of disturbances in function of the organ or upon some outstanding symptom. The present article would seem to add even greater confusion to the present-day mixture of anatomical, functional and symptomatic diagnoses of kidney disease. This is the chief

criticism of an otherwise extremely able presentation. Addis classifies Bright's disease as hemorrhagic, degenerative and arteriosclerotic. The first type is subdivided into initial, active, latent and terminal stages. The criteria upon which this classification is based are the number of red cells, the epithelial and white cells, the casts and the milligrams of albumin in specimens of urine. Collected under certain well-controlled conditions, and examined by the special technic of the author, neither the control of the patient nor the methods of examination of the urine apparently offers any serious obstacle to the physician; therefore, the simple and lucid classification of the author has distinct advantages. However, until the methods of the author are extensively used and found practical to use it would not seem wise to employ the new classification of Bright's disease in textbooks, current literature or in the teaching of students.

Puncture of the Cisterna Magna: A Summary of Four Years' Experience.—Puncture of the cisterna magna was first described by Ayer, in 1920, as a clinical procedure of value in certain cases of meningitis. F. G. EBAUGH (*Jour. Am. Med. Assn.*, 1925, 85, 184) promptly saw the advantage of this method of securing cerebrospinal fluid or of introducing therapeutic agents into the canal, and has employed it extensively the past five years in his neurologic work at the Philadelphia General Hospital. The present paper is a general report of the 1550 punctures of the cisterna magna in a total of 190 patients that the author has done in the above mentioned time interval. He states that after a certain amount of practice on the cadaver the operation is easily and readily performed. In all his cases only 2 patients showed any possible but questionable ill results after the puncture. Forty patients were examined after death without evidence of pathologic changes, and 1 of these patients had 26 intracistern injections. The clinical indications for puncture of the cisterna magna are summarized by the author as (1) therapeutic, (2) diagnostic and (3) prophylactic. Under the first head is included 1340 punctures for the purpose of injecting arsphenaminized and tryparsaminized serum in treatment of general paresis; 32 injections of antimeningococci serum in 8 advanced cases, with recover of 5 patients; 54 punctures for therapeutic drainage; 2 punctures for the unsuccessful treatment of a patient with tetanus. Under diagnostic use of cisterna puncture are listed 20 punctures in 15 cases of which 7 showed definite findings of spinal block verified at autopsy or operation; 3 punctures for the localization of spinal-cord tumors through use of lipiodol; 4 cases for the localization of site of hemorrhage; 27 cases in which lumbar puncture was impossible. The prophylactic use of this procedure is to prevent possibility of block following meningitis. In discussing more in detail these figures the author writes that the use of arsphenaminized serum in the treatment of neurosyphilis has been discontinued on account of the failure to achieve any beneficial effects. He says that the treatment of meningitis by alternate intraspinal and intracistern puncture offers a method of getting the greatest concentration of serum into the cerebral and spinal subarachnoid space and avoiding subarachnoid block. This suggestion, and it is largely a suggestion as the author has not had the opportunity of trying out this procedure at all extensively, is apparently an extremely practical one.

SURGERY

UNDER THE CHARGE OF

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A Critical Study of Endocrine Therapy in Gonad Failure in the Male.—LAWRENCE (*Boston Med. and Surg. Jour.*, 1925, 192, 480) noted that the clinical picture produced by ablation or depression of the endocrine function of the male gonad is not constant. The variations are probably due largely to the age at which the failure occurs. Eunuchoid states are frequently due to secondary gonad failure which is a result of some other endocrine dysfunction, notably the pituitary. The treatment of such conditions by use of testicular extracts or implants cannot be expected to give good results. Therefore, every patient showing eunuchoid symptoms should be carefully examined for evidences of other endocrine disease before testicular organotherapy is advised. If such treatment is indicated it is best obtained by implantation of human testicular substance. The treatment of such conditions as senescence, sex lassitude, dementia precox, epilepsy or general asthenia by gonadal extracts has no logical basis and is not at present justifiable. There is no definite evidence that the use of testicular extract in tablet form has any specific effect in man. Endocrine therapy of gonad failure in the human male cannot become an established form of treatment until the effects of such failure upon bodily processes has been determined by objective measures and the value of therapy proven by demonstrating its effects in the same way. At present the conditions for which organotherapy is indicated are limited to the results of castration and certain eunuchoid conditions.

Is there an Essential Hematuria?—SCHEELE and KLESE (*Arch. f. klin. Chir.*, 1925, 130, 388) state that this concept has lost its significance in the light of newer pathologic, anatomic and clinical observations. Bleeding in the parenchyma comes from glomerular and interstitial sources. The areas of the papillæ and pelvis have mechanical inclination or disposition to bleed, due to the arrangement of tissue elements. The rich subcapsular lymphatic network offers definite cause for bleeding from the capsular area. For bleeding to arise from nerve origin there are the peristaltic movements of the capsule and the definite hyperemia of the kidneys under nervous influences as factors. The mechanical interruption of the kidney circulation either through venous pressure or back pressure of the urinary tract, can lead to hemorrhage. There is blood from the kidneys in hemophiliacs. This hemorrhage however, is present only in men who show the other signs of hemophilia. Hemorrhage and pain show no typical course, therefore

they are not significant alone for diagnosis. The authors analyze the conservative and radical operative procedures at length. Only in life-destroying hemorrhage, do they feel that primary nephrectomy is indicated.

The No-foreign Body and Tight-fitting Window-cast Technic in Open Reduction of Fractures.—SORESI (*Jour. Bone and Joint Surg.*, 1925, 7, 289) states that open reduction of fractures by the no-foreign body and tight-fitting window-cast technic represents an advanced step in the treatment of fractures. In the cases in which the method was applied results have been very satisfactory; none of the complications common to the other methods of open reduction, such as infection, osteomyelitis, necessity of removing the foreign bodies used for osteosynthesis, delayed union, painful limbs or death were observed. In cases where infection was present no unpleasant complication was noted. The results were as satisfactory as in the clean cases. This fact demonstrates that complications noted where other methods are followed are due to the presence of the foreign bodies used in the process of osteosynthesis. It follows that foreign bodies prevent the proper formation of callus and favor infection, while direct good coaptation of the fractured ends of the bone, presence of blood, complete absence of foreign bodies in the wound mean better union, because callus formation is not hindered. Contrary to the generally accepted opinion, bones can stand a great deal of trauma and infection, the ordinary usual complications following trauma and infection being due to the presence of foreign bodies which are injurious to the process of bone repair.

On the Viability of the Intestine in Intestinal Obstruction.—ELSBERG (*Ann. Surg.*, 1925, 81, 926) believes that it is often difficult to determine the viability of strangulated intestine, although there is a rich anastomosis in the mesentery and intestinal wall, comparatively slight interference with this circulation causes disproportionately great damage to the intestine. Experimental ligation of the vessels of the second mesenteric arcades is the safest. The circulation returns or becomes reestablished in an impaired segment either through the temporarily occluded vessels, or as the result of a collateral circulation. The circulation does not return and the segment becomes gangrenous if the involved area is too large and there is too great a trauma to the vessels with a prolonged spastic muscular contracture. The classification of strangulated bowels into early, intermediary and late does not designate units of time. This depends upon the size of the segment, its proximity to the duodenum and whether the circulation is immediately or gradually occluded.

Syphilis of the Urinary Bladder.—SAELHOF (*Jour. Urol.*, 1925, 13, 461) says that the pathological anatomy of vesical lues has been studied by suprapubic cystotomy, cystoscopic examination and autopsy. It may be readily apprehended that the pathologic anatomy evident in the bladder wall is essentially dependent upon the stage of the disease in general. In the author's case the intensely hyperemic mucosa with ulcerations eccentrically located about the mouth of the left ureter led to a diagnosis of syphilis of the bladder. Under intensive antiluetic

therapy the bladder symptoms disappeared. However, under the delusion that he was cured, the patient failed to continue treatment and a subsequent relapse with return of bladder symptoms again became manifest. Death ensued from a bronchopneumonia complicated by cerebrospinal lues. Microscopic sections of the bladder revealed a picture essentially that of lues of any organ of the body, namely a marked proliferation of lymphocytes and round cells, proliferation of fixed cells and more or less endarteritis.

Abdominal Torsion of the Omentum.—COWELL (*Brit. Jour. Surg.*, 1925, 12, 738) declares that torsion of the omentum is commonly associated with the presence of hernia. True intraäbdominal torsion, however, does exist, although it is rare. The following simple classification of torsion of the omentum is suggested by the author: Abdominal; primary, with no apparent cause present; secondary, associated with disease of an abdominal or pelvic organ; hernial: (a) intersaccular, (b) intraäbdominal, (c) combined. Clinical recognition is possible and operative treatment successful. The pathogenesis is uncertain, but obesity is a factor in some cases. Torsion of the omentum should be one of the conditions suspected when a rush of blood-stained serum occurs during a laparotomy on an acute or subacute abdomen. The adhesions readily give away and the mass is easily removed by ligaturing the pedicle. The mortality is low, namely 5.5 per cent, and no complications have occurred in the author's series of 18 cases.

Carcinoma of the Rectum Complicated by Pregnancy.—MAUNSELL (*Brit. Med. Jour.*, 1925, 3357, 826) claims that there are two "schools" of rectal surgery. One advocates the perineal route for excision, while the other despises anything except the combined abdominal and perineal operation. The author feels that the two-staged operation is much easier and feels that it is the method of choice where pregnancy is a complication, unless there is some special reason for the one-staged operation. The author feels that the incision through the left rectus is best for colostomy, either with or without a median incision for the exploration. With regard to the treatment of carcinoma of the rectum in general, the author sometimes uses the combined method, but more often the perineal, with removal of the coccyx and the last segment of the sacrum, a thorough exploration and a colostomy having been made some days previously. He is convinced that the mortality of the combined method is very much greater than that of the two-stage operation, while the percentage of "cures" is not more pronounced in one group than the other. The author's teaching is to remove the growth by the two-staged method, when it is in the portion of the bowel which has no mesentery. When the growth is situated higher up it is better to remove it by the combined method.

Elbow Fractures and Dislocations.—SIRIS (*Surg., Gynec. and Obst.*, 1925, 40, 665) claims that children have excellent reparative powers in fractures. Perfect anatomic approximation of the fragments is not always essential for functional recovery. Displacement and overriding of fragments will often result in a good functional limb and complete restoration of the bony contour. Anatomically restored elbows may

be lacking in mobility unless they are treated judiciously. The best results are obtained by immediate reduction under an anesthetic with the aid of the fluoroscope. Partial immobilization with adhesive and early active motion will reduce swelling, increase muscular toxicity and prevent muscular spasm, exuberant callus, Volkmann's ischemic paralysis and myositis ossificans. Passive motion with or without an anesthetic and active massage retards progress. Musculospiral and ulnar paralysis accompanying the following fractures about the elbow is now always permanent. Myositis ossificans will disappear with the discontinuation of trauma to the brachialis anticus. Open operations in children are not indicated, as good functional limbs will follow displaced fragments and infections are very prone to follow open operations. Compound fractures are best treated by debridement. Carrel-Dakin sterilization, suspension in flexion by adhesive or in a flexed Thomas splint, to be followed by secondary suture or granulation with the institution of early active motion.

Movable Kidney.—MATHÉ (*Surg., Gynec. and Obst.*, 1925, 40, 665) states that the great majority of movable kidneys cause no symptoms and require no treatment. In a certain percentage of cases, however, renal mobility forms a definite clinical entity characterized by lumbar pain, urinary, gastrointestinal and nervous disturbances, loss of weight and require fixation by abdominal support or surgical intervention. The condition is more common in females because the renal fossæ are shallower, cylindrical or even funnel shaped, being wider below than above. The predisposition to displacement is increased at puberty because of the widening of the bony pelvis. In males the renal fossæ are pear shaped, being narrower below. Its greater frequency on the right side is due to the shape of the renal fossa, the presence of the liver on that side and the weaker support afforded by the less well-developed right, perirenal fascia. The majority of cases of renal ptosis can be relieved by the proper abdominal support, fattening and strengthening exercises. Nephropexy is a justifiable operation and is indicated in conditions not relieved by more conservative measures. The author has employed nephropexy in 30 cases, with successful results in 96 per cent of the cases; 46 per cent of these cases had obtained no relief from mechanical supports. A review of the literature leads the author to believe that surgical suspension has fallen into disrepute, not on account of its inefficiency, but because it has been performed when it has not been indicated. Moreover there is often failure to realize the necessity of exposing the ureter and relieving any condition which might be present, which unrelieved would defeat the purpose of the operation.

The Treatment of Acute Pathogenic Joint Infections.—BLAKE (*Am. Jour. Surg.*, 1925, 39, 81) states that the story of the treatment of pyogenic arthritis resembles in many ways that of suppurative peritonitis and empyema of the thorax. Surgeons now know that the same principles apply to the treatment of all cavities. These concepts are in the main: That resolution usually follows if the origin or cause of infection is removed before pathologic changes have taken place in the deeper tissues. Traumatism, leading to death

of tissue, prolongs suppuration and prevents resolution. Foreign bodies, such as drains, produce traumatism. Accumulation of the products of infection not only delay absorption, on account of their bulk, but by pressure in the rigidly enclosed cavities, such as joints, interfere with circulation and may cause thrombosis of vessels and necrosis of tissue, not to speak of toxins from the exudates. When suppuration of a joint is produced by extension from a focus in a bone or from an infected fracture implicating the joint it is obvious that the primary lesion in the bone must be well-laid open and drained, so as to prevent, so far as possible, contamination of the joint. Such joints should be kept at rest to prevent spreading the infection throughout the articulation. In the case of the knee the condition may become formidable and amputation should not be deferred to the point of danger to life. This amputation should be done in two stages to avoid the danger of osteomyelitis of the stump. The author describes in generalities the treatment of primary suppurative processes in joints, stressing as the ideal time the first twelve hours after injury, in which there is practically no pullulation of bacteria, and a thorough trimming away of contaminated and devitalized tissues will prevent infection or modify its virulence. No drain should be used. Early active movements should be instituted in joints where mobility is desirable.

PEDIATRICS

UNDER THE CHARGE OF

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Supervision of the Dairy Herd to Prevent Anaphylactic Symptoms in Infant Feeding.—ROHRBACH (*Atlantic Med. Jour.*, 1925, 29, 670) has been unable to find anything written on this subject in any of the available indices. Evidence that cow's milk produces anaphylaxis is admitted by many eminent authorities. These symptoms are referable to practically every tissue of the body. The family history often reveals a characteristic hereditary tendency to be sensitive. Cow's milk is tolerated with great difficulty by 15 per cent of well and sick infants. This intolerance is manifested by a positive skin reaction in some infants and a negative one in others, whether artificially fed or breast fed. If allergic disturbances are changes in the physical and chemical mechanism of the blood and tissues, thereby bringing about an altered state of physiologic functions then it is believable that similarly the food of the dairy animal producing milk for infant feeding is a source of frequent anaphylactic symptoms and that the clinical symptoms of the cases reported in this paper are typical allergic reactions to such foods. It is a sad but true fact that no interest at all, it might be said, is taken by the medical profession in the production of milk for human consumption.

The Ketogenic Diet in Epilepsy.—PETERMAN (*Jour. Am. Med. Assn.* 1925, 84, 1979) used the ketogenic diet which consists of a large amount of fat with minimal amounts of protein and carbohydrate. The object of the diet is to produce a ketosis as evidenced by acetone and diacetic acid in the urine. It is especially desirous to stress this objective. He treated 37 patients with essential epilepsy for periods of from three to thirty months by means of this high fat diet sufficiently restricted in carbohydrates and proteins to produce ketosis. In 2 patients no change was noted. One patient improved while under control but was lost from observation. Three patients remained free from convulsions for from three to eight months, and were not heard from. Twelve had improved and 19 had been free from attacks since the institution of this treatment. Thirty-two still remained under observation at the time the report was made. The general physical development and growth had also been normal and exceptionally good in some cases. Resistance to infection seems no way diminished by this form of treatment. It is too early to offer an explanation for these results. Much work is necessary, and a better understanding of ketosis is essential. The theory under which this high fat treatment of epilepsy was first proposed was that aceto-acetic acid should behave pharmacologically as an anesthetic and reduce the reactivity of the nerve cell. It is sufficient to say at present that ketonuria with the high fat diet is a practical guide to treatment, even though it is not the only factor concerned in metabolism. Acidosis is possibly a factor in controlling the attacks. There is considerable evidence that the convulsions of epilepsy are associated with a metabolic disturbance. The capricious and inordinate appetites, the chronic constipation and history of stomach troubles and of food reactions, the periodic recurrence of attacks, the nature of status epilepticus, the increased toxicity of the urine obtained during the attacks, and in women the cessation or the primary appearance during pregnancy, all suggest coincident, if not primary metabolic disorder. Perhaps the most convincing evidence of metabolic disturbance is the response of the epileptic patients to treatment. In the earlier cases of pure idiopathic epilepsy in children the response to the treatment with ketogenic diet was striking. The results obtained by hydrotherapy, purging, by regularity of daily habits or best by a combination of all these adjuncts need no further mention. Psychotherapy is not to be overlooked.

Diphtheria of the Skin.—WARREN and SUTTON (*Jour. Am. Med. Assn.*, 1925, 84, 1983) report the case of a boy, aged five years, in whom the skin lesions of varicella took on an impetiginous character and became infected with *Bacillus diphtheriae*, probably transferred from the nostrils by scratching. They gradually progressed to extensive hemorrhagic crusted lesions covering about 49 sq. cm. of body surface. Death apparently was due to toxemia, and the necropsy findings were consistent with infection with *Bacillus diphtheriae*. Virulent diphtheria bacilli were recovered from the skin at least in one lesion, and the histologic picture of the lesion is that of diphtheritic ulceration. Sections stained by the Gram-Weigert method showed bacilli morphologically resembling *Bacillus diphtheriae*. In short in this case there were the microscopic findings consistent with toxemia due to infection

with the diphtheria bacillus, together with typical diphtheritic ulcerations of the skin. In addition, the recovery of virulent diphtheria bacilli from the nostril and from one of the skin lesions definitely stamps the case as one of diphtheria. The virulence of the bacilli was determined by the intracutaneous method. The guinea pig on whom the virulence test was done died on the fifth day after inoculation. Necropsy on this animal showed that death was due to diphtheria. The control pig protected by 1500 units of antitoxin was not affected. The Schick test was done on this case on admission, and was negative. This is a surprising finding in view of the subsequent death from diphtheria. The absence of membrane in the nasopharynx and the development of symptoms only as the skin lesions became infected led the authors to believe that the toxemia resulted from the diphtheria of the skin. Some of the lesions of varicella in all probability were infected from scratching with fingers that were infected with virulent bacilli from the nose.

Cerebrospinal Fluid in Syphilitic Children.—VON GUTFELD and MEYER (*Arch. f. Kindhk.*, 1925, 76, 13) made systematic examinations of the blood and cerebrospinal fluid in 155 syphilitic children, and they found a Wassermann reaction parallel to the clinical findings only in a part of the cases. In cases of mental and nervous disturbances a positive reaction was found in the cerebrospinal fluid more often than a negative, but the reaction may be positive without such disturbances or *vice versa*. Positive blood tests usually correspond to a positive reaction in the cerebrospinal fluid, but the reverse does not hold true. The colloidal gold test in the fluid elicited a reaction parallel to the Wassermann test in almost every case. Endolumbar treatment was never used. The clinical findings alone afford definite indications for treatment.

Congenital Hypertrophic Pyloric Stenosis.—BOLLING (*Jour. Am. Med. Assn.*, 1925, 84, 20) reviews 454 cases in which the Fredet-Rammstedt operation was performed. As to diagnosis, he feels that if the condition is kept in mind the diagnosis may be made promptly in almost every instance, and is not a matter of opinion but is demonstrable. A palpable pyloric tumor and a gastric peristaltic wave in combination occur in no other condition. The history if obtained from an intelligent nurse or mother is valuable and often typical. There has been some discussion as to the diagnostic value of the tumor. The author thinks it is the most important sign. The palpation of the tumor is most easily carried out after the stomach has been emptied by means of a soft rubber catheter, and while the child is kept quiet with its usual feeding or a sugar pacifier. Usually lying to the right hand of and above the umbilicus, the nodule may be made out high up under the liver or even in the midline, just below the ensiform cartilage. It is a small, oblong, movable mass, about the size of the distal phalanx of the little finger, and imparts a sense of almost cartilaginous hardness through the abdominal wall. The consistency of the tumor varies as the muscle comprising it is contracted or relaxed. At the

time of relaxation the pylorus may be stimulated by gentle kneading with the finger. The more emaciated the infant, the more obvious the tumor. In early cases in which there has been little loss of weight it is more difficult to make out, but patient examination will almost invariably be rewarded. In the 454 cases operated on it was felt in every instance but 1. During the same period there were 3 cases in which anteoperative diagnosis of a tumor proved incorrect. Deep, regularly occurring peristaltic waves, passing from left to right, may be seen in practically every instance if the epigastric region is inspected after the stomach is filled and while the child is quiet. These waves were observed in all but 3 cases of the series. Congenital occlusion of the duodenum may give a similar picture, but this condition is rare, and the presence of symptoms from birth and the bilious character of the vomitus serve to differentiate it from the pyloric involvement. The significance of peristalsis depends on degree. Slight peristaltic waves may be seen in even normal infants. The characteristic projectile vomiting is frequently observed during the examination. The secondary symptoms of loss of weight, constipation and scanty urine are merely evidences of starvation. The author thinks that roentgen-ray is indicated only in doubtful cases. Fluoroscopic examination is the most important means of making an accurate diagnosis and it not only shows whether the condition is pyloric stenosis, but classifies it immediately as a medical or a surgical case. It was found from a study of this series that the Fredet-Rammstedt operation is simple, curative and permanent in its result. Convalescence is rapid, and the infant returns almost at once to normal development. The constant progressive decline in mortality suggests further improvement in this direction. He feels that as a result of the finding in this analysis that there is no justification for delay which turns a good operative risk into a bad one substitutes a long accidental convalescence for a brief, uneventful one, and fails to restore the growing infant to a satisfactory state of nutrition at an important period of its development.

Tuberculous Meningitis in Children.—HERBEN and ASSERSON (*Am. Rev. Tuberc.*, 1925, 11, 184) made a very careful analysis of all the circumstances and facts connected with a series of 135 cases of tuberculous meningitis in children. In almost all of these cases the cause of the disease was the human type of tubercle bacillus derived through the child's contact with persons suffering from active tuberculosis. This form of infection is most prevalent in the least sanitary and most congested districts, and tenement houses present a most formidable aspect among etiologic factors. The evidence is predominately against milk infections as a cause of tuberculous meningitis in New York City. Otitis media and acute infectious diseases, especially measles, pneumonia and whooping cough in children in contact with active tuberculosis, carry a great menace. About 9 per cent of these 135 cases were preceded by tonsillectomy, unassociated with any other disease. Sex is not an important factor, males being only slightly in preponderance. The highest mortality occurred in young children, the greatest number of cases in a single age period developing in childhood from one to two years of age. In terms of absolute numbers only,

outside of the American stock, there was more tuberculous meningitis among the Italians than in any other racial group. While this study verifies the accepted view of the great prevalence of tuberculous meningitis in the spring, this disease among the Jewish and negro races reached its peak in midsummer. In 47 specimens of spinal fluid showing tubercle bacilli the latter were bovine in type in only 3 instances

GYNECOLOGY

UNDER THE CHARGE OF

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Irradiation of Benign Uterine Tumors.—About three years ago in the Cleveland Clinic, according to PORTMANN (*Jour. Iowa State Med. Soc.*, 1925, 15, 3), they began the investigation of deep roentgen-ray therapy. In collaboration with the department of biophysics a special study of the intensities of roentgen rays was made, and the findings were compared with the results already published. They were disappointed to find that the very great dosages anticipated were not obtainable under practical working conditions, and as a result they came to the conclusion that in most cases a therapeutic dose of radiation could not be safely administered to the most deeply situated malignant tumors by roentgen ray alone. The favorable results of radium therapy and this knowledge of the limitation of the roentgen ray led them to adopt a plan for the establishment of "a radiation therapeutic dose" by means of the combination of these two similar agents. This is accomplished by individualizing the patient by drawing on paper an exact cross-section of the body at the site of the lesion, and indicating thereon the involved areas and organs. Their own charts which show the rate of absorption of roentgen ray or equal intensity curves are superimposed on the cross-section at suitable portals of entry, so that the sum of the intensities of the roentgen rays which reach any point from the various portals may be calculated. A standard chart showing the sphere of radium activity is then superimposed at the point of radium application and the combined radiation from the roentgen rays, and radium can be computed for any point in the cross-section. By this method they are able to estimate and tabulate the exact dosage of radiation administered in any case. They have found that chronic metritis and fibromyomata react very favorably to proper administration of radiation in properly selected cases. Until recently the results of radiation in these cases have varied considerably, but since they now have accurate methods of measurement, and a basis for the selection of cases, they anticipate

more uniformity of results. In the selection of cases they believe that no woman under forty years of age should be subjected to radiation, as it tends to advance the menopause, although in certain cases there may be justifiable reasons for disregarding this precaution. Intensive radiation in the presence of chronic or acute inflammations or any evidence of inflammation within the pelvis is hazardous. Irregularity of the menses or the character of the bleeding may indicate a malignant or inflammatory degeneration of the uterus or of the tumor which would require a different method of treatment. A tumor of any size may be reduced by radiation, but those tumors that extend as high as the umbilicus may regress too slowly to relieve the rather distressing pressure symptoms. Pedunculated and subserous fibroids obviously demand surgical treatment. Pregnancy contraindicates radiation, as abortion will probably be induced, and it has been demonstrated that radiation may produce a monstrosity of the fetus. After eliminating the groups of cases indicated above as unsuitable for radiation there remain about 30 per cent of all cases of fibromyomata that may be safely treated by radiation. Relief of symptoms may be anticipated in 99 per cent of properly selected cases, and the percentage of complete cures averages about 87 per cent.

Cautery Treatment of Endocervicitis.—The use of the electrocautery in the treatment of chronic endocervicitis is surely enjoying increased popularity, judging from the number of enthusiastic reports which are appearing in the literature. One of the proponents of this therapy is DAVIS (*Surg., Gynec. and Obst.*, 1925, 40, 568), who describes his technic as follows: After inserting a suitable bivalve speculum the mucous discharge is thoroughly removed with cotton balls. A suitable nasal cautery tip, preferably one longer than usually supplied, is placed firmly against the tissue to be destroyed and the current turned on. As a sufficient depth is reached in the cervical tissue along the cervical canal, the tip is gradually moved so as to make a line through the diseased tissue. In many cases it is only necessary to cauterize the glands near the external os; in others the disease extends to the internal os. If at any time the patient complains of discomfort the contact button is immediately released and the current not applied again until she is comfortable. This process is repeated until a sufficient number of cautery lines have been made. Nabothian cysts are destroyed in a similar manner after puncturing with the heated tip. An effort is made to reach the depths of the glands so as to destroy the chronically diseased tissue. Most cases of endocervicitis may be treated in the office. One thorough cauterization results in early relief from most of the symptoms, and complete healing is usually found after six to eight weeks. If the first treatment is very superficial another may be needed after four weeks. Very few patients will need more than two treatments with the cautery. As a rule, it is advisable to administer an anesthetic (gas and oxygen) to virgins, women who are very nervous, or those who require unusually deep cauterization, due to the long duration of the endocervicitis. It may be difficult at times to remove tissue for examination unless the patient has an anesthetic. After a cautery treatment the patient is instructed to wear a pad until the increased discharge stops, which is usually in about ten days or two

weeks. She is also warned that the next period may be more profuse than normal, occasionally so severe as to require a pack for a few hours. Douches are advised against but the patient is advised to keep herself clean by external washing. The cervix is painted with 5 per cent mercurochrome solution every week until healing is complete. Sex trauma should be avoided during the period of convalescence from the cauterization.

Residual Urine in Women.—Previous to 1915, states CURTIS (*Surg., Gynec. and Obst.*, 1925, 40, 689), when he first called attention to the frequency of residual urine in women, his patients had much trouble with postoperative urinary tract infection. After 1915, upon realization of the importance of residual urine, he instituted the present plan of postoperative treatment with most satisfactory results. Under his plan of treatment the use of the catheter is avoided when possible, but no patient is allowed to suffer from distention. Failure to urinate within several hours after return from the operating room is not, in itself, sufficient reason for catheterization; distress should be the chief indication. It is true that marked distention should be relieved, but this does not often occur in the absence of notable pain. Provided the catheter has not been required, the presence of some residual urine for a few days is not a particular menace. Patients who require repeated catheterization almost invariably fail to recover immediately the power of complete evacuation upon resumption of spontaneous micturition. There usually ensues a period of several days, during which residual urine is present, and it is the daily withdrawal of this residual urine which is responsible for the present improved results. Catheterization, immediately after urination, preferably with slight bladder lavage, should be repeated once each day until residual urine disappears. Instillation of a small amount of antiseptic solution before withdrawal of the catheter, for example, $\frac{1}{2}$ ounce of 0.5 per cent mercurochrome is a helpful adjunct, together with urinary antiseptics by mouth. In contrast with previous experience, Curtis now finds that persistent postoperative urinary-tract infections have disappeared. Temporary mild cystitis may occasionally occur, but this is promptly disposed of. The much-dreaded "catheter" cystitis and pyelitis have been eradicated. We have followed this method of the author for some time in our department with very satisfactory results.

Value of Radiotherapy in Uterine Cancer.—According to W. J. MAYO (*Minnesota Med.*, 1925, 8, 7) radium has had its greatest triumph in the treatment of cancer of the cervix uteri. In the favorable cases radium is not only a compeer of the knife, but in the advanced case, when the vaginal fornix or the broad ligament is involved, it is the treatment of choice. The rays affect the embryonic cells with special vigor, while the sound tissues, such as the ureters, are little affected. On the contrary, in cancer of the body of the uterus, taking good, bad and indifferent cases, surgery cures from 70 to 80 per cent, and radium and roentgen-rays produce poor results. It has been a common experience in the clinic that even after radium had been used by experienced men in the body of the cancerous uterus for prolonged periods it was eventually necessary to remove the uterus, because some part of

it still contained malignant tissue. Unfortunately, the question of the curability of cancer is too often academic, because of the very large number of incurable cases that reach the surgeon, in which palliation is the utmost he can achieve. Here radiotherapy is, at its best, a triumph and a despair. It often does so much good that the family and the patient begin to look for and expect cure, but death, not cure, comes eventually, and radiotherapy is unjustly brought into disrepute after a meritorious performance. An unpleasant part of this discussion concerns the persons who are to use radium and roentgen-ray for the cure of cancer. When this work is done by men of wide experience, associated with an experienced surgeon and a competent pathologist, radiotherapy has great value. Today a large number of men with a small amount of radium, or with a roentgen-ray machine, are treating operable cancers or as has been said "With a nickel's worth of radium a million dollars' worth of harm can be done." The use of radium and roentgen-ray for therapeutic purposes is as much a specialty as surgery, but in the hands of the inexperienced, or of those who depend on the clinical diagnosis of the disease, it becomes a menace.

Stricture of the Ureter.—In a very well-prepared paper PUGH (*Ann. Surg.*, 1925, 81, 839) states that a real stricture of the ureter is a definite, permanent, pathologic intraureteral obstruction which is present at a particular location and never varies from it, and is demonstrable not only by means of specially prepared catheters or bulbs, but by ureterograms as well. He insists that there is such a thing as ureteral spasm, which may simulate stricture and at times will interfere with examination. At times the resistance of these spasms is so great as to make us think that they are strictures, but a little pressure usually overcomes them. In discussing the etiology of ureteral stricture, the author divides the causes of stricture into the traumatic, into that caused by other infectious processes, the so-called focal infections, and that due to direct extension of disease processes. Traumatic strictures are most commonly incident to childbirth injuries or the performance of extensive gynecologic operations. The discussion of focal infections has been most extensive. If practically every acute infection may produce a lesion in another organ, there is no reason why it should not occur in the ureter. One of the predisposing diseases especially emphasized by Hunner is tonsillitis. In almost all of the cases in the author's series there was a record of some previous acute infectious process. Although Hunner does not lay much stress on the gonococcus as a cause, from the author's experience it is his opinion that the extension of a gonorrheal process from the urethra to the ureter is, at least in the majority of cases, by continuity of tissue and not by lymphatic conduction. In these cases the sequence is urethritis, trigonitis, ureteritis and stricture. It is not his intention to state that the gonococcus is the most common cause of ureteral stricture, but he believes that it is no uncommon factor in that disease. The symptoms of ureteral stricture are pain, which may be sharply localized at the point of stricture or over the kidney, the latter often being due to back pressure. There is often frequency and urgency of urination, and sometimes vesical or even rectal tenesmus may be present. Hema-

turia may be present, especially during severe attacks of pain. In some patients the pain is of a dull, aching character and present constantly, but the other and more common type is the periodic paroxysms. The referred group of symptoms are usually gastrointestinal. Chills and fever are common, particularly where there is distinct evidence of urinary infection. The main factors in establishing a diagnosis of stricture of the ureter are a careful history, the pyeloureterograms and the therapeutic result of treatment. An interesting point which has caused considerable discussion of late is the relation of stricture to stone formation. Does stone cause the stricture or may not the stricture cause the stone? The author is sure that a stone descending from the kidney and lodging somewhere in the ureter would obstruct it, but that does not spell stricture. On the other hand, he is thoroughly convinced that stricture does produce stone. He states that in these days of careful investigation it is unthinkable to operate for renal stone without a thorough exploration of both ureters for stricture, and he believes that this procedure, by establishing good drainage, will save many kidneys and repeated nephrotomies. The prognosis in ureteral stricture can in general be stated as good. It however depends to a great extent on the etiologic factors involved. Where syphilis is the underlying cause the prognosis should be good with appropriate treatment. In tuberculous lesions the outcome will depend on treatment; local applications or dilatations are of no value, nephrectomy or nephroureterectomy being required. In the other forms of stricture the treatment consists of removing the cause if possible, and dilatation of the stricture through the cystoscope. In the use of ureteral dilators one should be careful not to dilate both sides (where bilateral stricture exists) at one sitting. Where this is done the trauma may produce contractions that will seriously delay treatment. Care must also be exercised that one does not puncture the ureter. The degree of dilatation necessary will depend entirely on the individual case, but we should dilate until we get good drainage which seems to be reasonably permanent. Operative treatment of stricture is unsatisfactory, and, like all other ureteral surgery, should only be resorted to as a final expedient.

Irradiation of Inoperable Cervical Cancer.—In describing the more recent methods of irradiation in the treatment of inoperable cervical cancer. DONALDSON (*Brit. Med. Jour.*, 1925, i, 876) says that, speaking generally there are two schools of technic: One which believes in external application only; the other which believes in burying the radium close to or within the growth. The arguments for the different opinions may be summarized as follows: The advocates of external application consider that any incision, even the introduction of needles, may disseminate the growth, and that the injured normal tissues may be affected by the radium to an undue extent, as it is well known that radium affects cells which are about to go into mitosis. They also believe that the tissue extracts produced by injury to the normal cells may stimulate the growth of the tumor and that the burying of needles may produce sepsis under conditions very suitable for the growth of organisms. Those authorities who advocate the burying of needles do not consider that these objections are in any way compar-

able to the advantages of the greater intensity obtained by placing the needles near the growth, and, further, that if the radium is used from the outside the doses have to be so large that there is considerable likelihood of damaging the skin and other intervening structures. The Radium Institute of Paris is inclined to believe in external application as is the Radium Institute in Stockholm, while in Brussels and most of the American institutes buried radium is preferred. In Great Britain the opinion is divided. The author's own opinion is that any technic should aim at getting a comparatively small intensity evenly distributed throughout the growth and applied for a comparatively long time. The question of the best dosage is still *sub judice*, but we must remember the fact that the intensity of radium obeys the inverse square law in the same way as does light. As an illustration, it may be noted that the dose received by the fingers holding a tube of radium with a filter of 5 mm. of platinum for a half minute is the same as if those fingers were exposed at a distance of one yard from the radium for a period of three and one-half years, or, to put it in a more practical form, the tissues in the pelvis 2 inches away from the tube receive 10,000 times less irradiation than the tissues immediately surrounding it. In regard to the duration of application, the author believes that the clinical evidence is very much in favor of a medium dose, well distributed and applied for a very long time, and in his last series of cases he has been using 50 mg. of radium element in twenty needles for one hundred and forty-four hours at a time, with distinct improvement in immediate results, compared with his former series. In analyzing his latest series of cases he finds that the hemorrhage ceased more or less permanently in 85 per cent, the ulceration disappeared in 63 per cent and in the cauliflower type the growth disappeared in 70 per cent.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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A Microscopic Study of the Excised Tonsil in Relation to Tonsillectomy.—Desiring to demonstrate the existence or nonexistence of the true "tonsil capsule;" whether or not the removal of the tonsil could take place without injury to or removal of some adjacent voluntary muscle tissue; the influence of the latter on the end-result of the healing, scar-tissue formation and deformity, as well as to briefly shed some light on the bloodless tonsillectomy, ISRAEL (*Ann. Otol., Rhinol. and Laryngol.*, 1925, 34, 79) studied, microscopically, about 500 sections from 172 tonsils, removed according to eight different methods by laryngologists of recognized skill in various parts of America. It was found that comparatively few tonsils were removed without some muscle tissue attached, the largest amount of muscle tissue appearing on the lateral surfaces of the atrophic type of tonsils in adults. Larger

tonsils, particularly in children, showed muscle tissue consisting chiefly of part of the palatoglossus and mucous membrane of the anterior pillar. No true capsule, which could be separated as a definite independent structure, could be identified as such. The amount and type of bleeding were found to be dependent chiefly on the anatomic development and distribution of the blood supply in the individual case rather than upon the instrument used for the tonsillectomy. The degree of postoperative discomfort and deformity were influenced by the quantity of contiguous muscle tissue removed at the time of operation. The author believes that the removal of small fragmentary fibers of muscle tissue is impossible to avoid and is of no clinical consequence. He concludes that the dissection method "Properly performed and under direct view, step by step, as the tonsil is enucleated, yields the greater number of complete removals."

The Fahraeus Blood-sedimentation Test in Otorhinolaryngology.—It is known that the sedimentation of blood is accelerated under conditions of marked protein disintegration and resorption, as in acute suppurative processes, when the acceleration is in direct ratio to the extension and severity of the inflammation. Applying the Fahraeus test to certain otorhinolaryngologic conditions, BERTOG (*Ztschr. f. Hals-, Nasen- u. Ohrenhllk.*, 1924, 10, 28) found that in acute suppurative lesions of the middle and external ear, and the accessory sinuses, the rapidity of sedimentation varied from 15 to 75 mm. The technic consisted of filling a 2-cc syringe, containing 0.4 cc of 2.5 per cent sodium citrate solution with blood. After mixing by centrifugalization the citrated blood was drawn into a 1-cc pipette of 3-mm. caliber, allowed to stand and the results read in forty-five or sixty minutes. The author believes the test has a particular field of usefulness in doubtful cases, but stresses the importance of serial tests, inasmuch as a single examination is inadequate because acceleration of sedimentation merely indicates presence of suppuration in the body.

PATHOLOGY AND BACTERIOLOGY

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Extensive Necrosis of the Liver in an Infant.—In recent years descriptions of necroses of the liver have commonly appeared in the literature and their incidence appears to be increasing. These liver necroses have largely been associated with infectious diseases and intoxications. In the majority of instances the character of the necrosis is unique and focal. The more extensive necroses, such as

are observed in acute yellow atrophy, have been described in adults as well as in children under a variety of circumstances, of which arsenic poisoning has come into prominence. In children the necroses of liver as they most commonly attract attention have been of small extent and usually associated with various bacterial infections, particularly those arising in the gastrointestinal canal. Acute yellow atrophy has also been described in children, but only occasionally has a severe necrosis been found in infants only a few months old. DEGENER and JAFFE (*Centralbl. f. allg. Path.*, 1925, 35, 556) report a case in a dead-born male child in which other than the presence of some anasarca and a slight amount of ascites nothing unusual was found in the remaining tissues of the body except the presence of extensive necroses of the liver. This appears to be the only case on record where such a lesion has been found in the newborn. The liver was of usual size and showed nothing other than necroses with a geographical distribution involving mainly the right lobe. These necrotic areas were plainly visible and sharply demarcated from the surrounding and otherwise healthy-looking liver structure. On microscopic examination there appeared to be a slight fibrosis in the liver, but the authors were unable to demonstrate the spirochete in this or other tissues. The authors were unable to determine the cause of the necrosis, although they suggest an undetermined infection. The extent of the necrosis as shown in an illustration suggests further the possibility that there was a marked circulatory disturbance in the liver and that this condition accounted for the necrosis more than the presence of toxins in the blood.

A Note on the Bacteriophage with Respect to Complement-fixation Tests.—Using beef extract bouillon and beef infusion bouillon to immunize rabbits SANDERSON (*Jour. Immunol.*, 1925, 10, 625) found that the sera of these animals possessed complement-fixing substances displayed in the presence of the homologous or heterologous antigen. He also found that the sera of 3 of 4 untreated rabbits contained this substance in just as high concentration as the sera of the treated rabbits. It was not present in the serum of the fourth rabbit nor in the sera of 4 calves, 1 guinea pig and 1 horse. The serum of a rabbit immunized with a broth culture of *Bacillus coli* dissolved by the action of a phage showed a comparable concentration of complement-fixing substance but this was demonstrable with either beef extract bouillon or *Bacillus coli* phage in broth as antigen. Similarly the sera of the untreated rabbits would fix complement using the *Bacillus coli* phage as antigen though calf serum failed to do so. It is concluded that rabbit serum commonly contains nonspecific complement-fixing substances demonstrable in the presence of bouillon as antigen. Also a possible fallacy in similar experiments of de Herelle which were used to argue for the identity of all bacteriophages, is demonstrated.

Isolation, Morphology and Cultural Reactions of *Bacillus Tetani*.—FILDES (*Brit. Jour. Exper. Path.*, 1925, 6, 62) describes a new method for the isolation of *Bacillus tetani* from mixed cultures and tetanic material. It was noted that *Bacillus tetani*, under suitable conditions, has a tendency to grow as a spreading, lacy film on the surface of a

medium, this characteristic being much more pronounced than with other anaërobes. Inoculation was made into the water of condensation of a sloped tube of agar, the growth spreading to the apex of the slant in one or two days. Contaminating organisms spread only to a minor extent. Septic blood agar was the medium used. Six specimens of material from human cases of tetanus were studied, and all 6 were found positive. Two hundred specimens of human feces, with 2 positive, 200 specimens of horse feces with 34 positive, and 70 specimens of soil with 33 positive, were the sources of the strains studied. In all, 75 strains positively identified as *Bacillus tetani* were investigated. The technic of isolation is described. The variation in the morphology of the organism impressed the author, particularly with regard to the spores. He claims that the typical "drumstick" form is idealistic and that the oval spore variously placed is met with under different conditions. A thorough study of the cultural reactions is reported; the opacity in blood broth appearing usually in the second day; indol from all of 70 strains in seven days; characteristics of shake cultures; feeble or absent growth in gelatin; no coagulation of milk; no fermentation of sugars; and evidence is given of a slight proteolytic action of the organism. The strains used have been deposited in the national collection of Type Cultures, Lister Institute, London.

Experimental Soot Cancer.—A method of extracting an active fraction from soot for the production of experimental carcinoma in mice is reported by PASSEY and CARTER-BRAINE (*Jour. Path. and Bact.*, 1925, 28, 133). Three fractions were prepared, one containing the ether-soluble substances in soot; one containing the ether-soluble bases and neutral substances and the third the ether-soluble bases of the water-soluble salts. Eighty young adult white mice were used in three groups comparable as regards color and size. The skin on the back was depilated and the fractions, diluted with ether were applied with camel's hair brushes, at first three times a week and later twice. Fractions 1 and 3 produced no cancer. Using fraction 2 on the 40 mice in one group, 18 survived until the eighty-eighth day and 16 of these had developed warts. Nine of the 18 showed malignant changes in from six to twelve months. As reported by other workers, initial mortality is high, ulceration, parasitic diseases and toxic states reducing the number of experimental animals about one-half. Protocols are given of each of the 18 animals mentioned. Fraction 2 was now investigated and was further fractioned by distillation in an atmosphere of coal gas into four distillates. By omitting scarification of the depilated skin, malignant tumors were produced by the application of the higher-boiling distillates. The authors conclude that an active-fraction of soot consisting mainly of ether-soluble bases will produce cancer readily in mice and that these carcinogenetic factors are distilled over in the fractions boiling above 190° C.

The in Vitro Cultivation of Tissues with Reference to the Production of Cancer by Means of Radium and Roentgen-rays.—An interesting study of experimental cancer is reported by MOTTRAM (*Brit. Jour. Exper. Pathol.*, 1925, 6, 53). It has been the custom to look for a stimulating factor in the cause of cancer. This work directs one's

attention to another possibility; that of the destruction of growth-inhibiting factors. Kidneys of rats were emulsified and extracted with Locke's solution at 0°C . Sets of cultures were prepared using plasma, embryo extract, kidney extract and kidney fragment and the cultures were incubated for three days. They were then fixed and stained and the extruded cells and mitoses were counted. It was demonstrated that a growth-inhibiting factor was extracted from old tissues but not from young and not from Jensen's rat sarcoma. Radiation experiments were carried out in vitro and in vivo. For the former, radium was used as the source of radiations. Details of the cultures and technic were given. For the in vivo work, both radium and roentgen ray were used, of which full details are given. In summing up, it was found that extracts made at 0°C . from the kidneys of adult rats inhibit the in vitro growth of kidney cells. Exposure of emulsified kidneys to 35°C . for one or two hours before the extract is made destroys the inhibitory factor. Exposure of emulsified kidneys in vitro to radium and in vitro and vivo to radium and roentgen rays likewise destroys this factor. The radiation effect was immediate and became progressively less as time was allowed to lapse between the radiation and the making of the extract.

Adenomyoma of the Stomach.—Case reports and discussion are presented of 5 cases of adenomyoma of the stomach by STEWART and TAYLOR (*Jour. Pathol. and Bact.*, 1925, 28, 195). It is considered as a heterotopia closely simulating clinically, a number of other diseases of more frequent occurrence, especially gastroduodenal ulceration. Grossly one finds a localized but ill-defined thickening, both visible and palpable, in the pyloric region of the stomach. From the peritoneal aspect the appearance may simulate an early pyloric cancer. The mucous membrane is normal. The cut surface shows whorling of the pyloric musculature with scattered cystic spaces of small size, or solid yellowish areas. The essential feature histologically, is the presence of glandular tissue both differentiated and undifferentiated. Unstriated muscle seems to form an integral part of the tumor. The paper gives minute details of the clinical course, morbid anatomy, histology of the 5 cases and a general discussion of gastro-intestinal heterotopias. The authors indicate that the condition is easily recognized in the gross and that upon identifying it, local excision is adequate treatment. Admirable plates facilitate the reading of the text.

The Incidence of Two Types of Group II Human Red Blood Cells.—KLINE, ECKER, and YOUNG (*Jour. Immunol.*, 1925, 10, 595) confirm the report of Guthrie and Huck, that individuals with Group II blood type may be subdivided into those whose cells contain agglutinin B and those whose cells contain agglutinogens B and C. By absorbing Group III serum with Group II cells containing only B, the serum was found to still promptly agglutinate the cells of 81 per cent of 200 Group II adults and the cells obtained from the umbilical cord of 51 per cent of 100 Group II newborn infants. It is concluded that the Group II cells which failed to agglutinate in the absorbed serum contained only agglutinin B while those which agglutinated contained agglutinogens B and C. The authors suggest that the agglutinin C is identical with the agglutinin X of Coca and Klein.

Innervation as a Factor in the Experimental Production of Cancer.—CRAMER (*Brit. Jour. Exper. Pathol.*, 1925, 6, 71) reports a study of 43 mice on which skin-autoplast or skinflap operations had been done. In one series an oblong piece of skin was completely removed from the back and then carefully stitched on again; and in another the flap was left connected with the unsevered skin by a narrow bridge. When healing was complete, after unsuccessful operations had been discarded, tar-painting was begun twice weekly in the center of the denervated area and on an area of normal skin. At the end of nine months, 12 of the surviving mice had developed tumors and 5 had remained negative. All 12 had tumors on the normal skin; 5 had also developed tumors on the denervated area. It is presumed that after two or three months, innervation of the denervated areas has taken place. Different areas of normal skin showed different susceptibilities to the tar-painting. The study shows that the presence of an efficient nervous control is an important factor in the process of chronic irritation leading to cancer formation. One cannot define as yet the part played by the nervous control.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Some Effects of High Environmental Temperatures on the Organism.—FLINN (*Pub. Health Repts.*, 1925, 40, 868) undertook his investigations to obtain a more intimate knowledge of the specific effects of high environmental temperature upon the individual organs and tissues of the body so that the more general effects as observed among men who are compelled to work where the air temperature is abnormally high could be more intelligently interpreted than has heretofore been possible. The following summary is given: "(1) During an exposure of six hours to an environmental temperature of 20° or 30° C. there was a drop in body temperature, probably due to a decrease in muscular activity. At 40° C. there was an increase of 1° in body temperature without an initial drop. At 45° and 50° C. the body temperature rose within an hour to such a height that it was deemed unsafe to continue the experiments. (2) The oxygen capacity of the blood showed no changes during the exposure to the different temperatures that cannot be accounted for by the diurnal changes in the hemoglobin or the concentration of the blood due to excessive evaporation of water. (3) The oxygen content of the blood remained

unchanged at 20° C., but showed a drop at 30° C., which is probably associated with the low rate of metabolism at this temperature. At 45° and 50° C. there is a slight increase in the oxygen content, due to the increased aëration of the blood at these temperatures; but this increase is not in direct proportion to the increased passage of air over the membranes of the mouth and throat. (4) At temperatures of 20° and 30° C. the alkali reserve remains unchanged, while at 40° C. there is a sharp fall during the first four hours, followed by a slower fall during the next two hours. At temperatures of 45° and 50° C. there is a rapid depletion of the alkali reserve from the beginning, which is almost identical for each of these two temperatures. (5) The carbon-dioxid content follows the alkali reserve, except that at 30° C. there is a slight rise for the same reason that the oxygen content falls. (6) The hydrogen-ion concentration of the plasma remains unchanged during an exposure of the animal to a temperature of 20° C., 30° and 40° C., but decreases at temperatures of 45° and 50° C., due to the excessive pulmonary ventilation at those temperatures with the consequent washing out of carbon dioxid without a compensatory loss of alkali from the blood. (7) The concentration of blood sugar falls during an exposure to temperatures of 20° and 30° C. This fall is probable associated with inactivity of the animal during the course of the experiment. At 40° C. it falls during the first two hours to increase during the following four hours. At 45° C. no change was noted during an hour's exposure, while at 50° C. there was a sharp rise during this time. (8) The blood solids at 20° and 30° C. showed only the usual diurenal changes. At 40°, 45° and 50° C. the concentration of the blood increases with the environmental temperature, no initial drop being seen. (9) An increased air movement benefits the organism by laying the deleterious effects, but apparently at the expense of the organism itself. (10) The free drinking of water during an exposure to high air temperature is of greatest benefit in maintaining the organism in a normal condition."

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ORIGINAL ARTICLES.

THE RELATIONSHIP OF THE SYMPATHETIC INNERVATION
TO THE TONE OF SKELETAL MUSCLE.

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[This essay was written for this Journal by the late Professor Hunter on board the vessel that brought him from America to England in November, 1924. His aim was to reply to the criticisms of his work that had been made during the previous two months in America and also to clear away certain misunderstandings. It was merely the first draft, but it is published here exactly as he left it without any alterations of any sort.—G. ELLIOTT SMITH.]

"It appears to me likely that reflex tonus is the expression of a neural discharge concerned with the maintenance of *attitude*." Sherrington, "The Integrative Action of the Nervous System," 1920, p. 340.

I. **Introductory.** It has been known since 1879 that striated muscle receives not only motor nerve endings from the thickly medullated cerebrospinal nerves, but also the terminations of non-medullated nerve fibers which form a rich plexus lying between the muscle fibers. Tchiriev, the discoverer of this fact, regarded these terminations, which are grape-like in appearance, simply as immature forms of the typical motor nerve endings. Consequently from the physiological standpoint his investigations did not excite a great deal of interest. But the fact observed by him that the "terminations en grappes" were connected with non-medullated nerve fibres

and the typical motor endings with medullated nerve fibres suggested that some specific difference existed between the two modes of innervation. Obviously, however, histological examination alone was not adequate to decide this point. For instance in 1913 Boeke suggested that the non-medullated fibres were sympathetic or autonomic in character. But it has been the application to this problem of the histo-experimental method by Boeke, Boeke and Dusser de Barenne and Agduhr which has proved beyond reasonable doubt within the last decade that the vertebral sympathetic ganglia are the source of these fibres. In other words the non-medullated nerve plexus is made up of post-ganglionic fibers of the sympathetic nervous system, the term "sympathetic" being employed here in the sense defined by Langley. It refers to the system of nerve cells and nerve fibres which have a connexion with the cerebrospinal axis limited to the thoraco-lumbar region. Fig. 1* represents schematically the principle of the operations employed by Boeke in investigating the source of the double innervation of the extrinsic muscles of the eye. In one series of experiments one of the motor cerebral nerves to the extrinsic muscles of the eye was removed near its point of emergence from the brain stem. Conversely, in the other series, the superior cervical ganglion was removed. While open to question in certain important details, Boeke's general interpretation of his results, namely, that some, at least, of the non-medullated nerve fibres supplying the eye-muscles are transferred to the oculo-motor nerves, by way of the cervical sympathetic trunk reaching the nerves distal to the point of emergence of these nerves from the brain stem, is unquestionably justified. Further a similar operation and its converse have been performed more recently upon spinal nerves. Boeke and Dusser de Barenne and Agduhr have both produced degeneration of all the medullated nerve fibres to certain muscles by section (of both anterior and posterior nerve roots) of the appropriate spinal nerves, while non-medullated fibres supplying these muscles remained intact. Conversely Agduhr found the remains of degenerated non-medullated fibres in preparations of the interosseous muscles of the cat's fore paw six days after removal of the ganglion stellatum.

It has been established therefore that striated muscle has a double innervation, *i. e.*, from the somatic cerebrospinal medullated nerves and from the sympathetic nervous system. The latter nerve supply consists of non-medullated fibres of cells in the vertebral sympathetic ganglion which reach the spinal nerve by way of the grey rami communicantes. Impulses from the cerebrospinal axis proceed to the sympathetic ganglion by way of the white rami communicantes which arise in the thoraco-lumbar region.

* Although no figures accompanied the manuscript, the text is left unaltered so that the article may be entirely Dr. Hunter's. There are indications that a bibliography was intended, but it has not been supplied for the same reason.—Ed.

The non-medullated fibres and their endings are independent of the sympathetic terminations upon the bloodvessels supplying skeletal muscle. Sometimes, it is true, they accompany arterioles to the muscle, but as they approach their site of termination they proceed to the muscle fibres entirely independently of the vascular plexus, as Dr. Oliver Latham and I have shown in a memoir now being prepared for publication.¹

II. The Function of the Sympathetic Innervation of Striated Muscle.
 In 1913 de Boer, as the result of experiments upon frogs, claimed to have shown that the sympathetic nerve supply of skeletal muscle was concerned with tone. He believed that the tone of striated muscle was governed exclusively by its sympathetic nerve supply. All subsequent workers have shown that this contention is untenable. De Boer's view is being replaced by the conception that only a certain element of muscle tone is due to the sympathetic nervous system. In 1915 Langelaan advanced the view that the tone of skeletal muscles consists of two elements, one component being governed by the somatic supply and the other by the sympathetic innervation of the muscle. This suggestion was put forward independently by Revon. Later, Langelaan (*Brain*, 1922), as the result of experiments on frogs adduced further evidence in confirmation of his opinion. He failed, however, to clear away the fundamental objection to the acceptance of his theory, namely, that no investigator had shown tone to be altered consistently in decerebrate preparations as a result of sympathetic denervation; or, conversely that decerebrate rigidity could develop if the sympathetic innervation were left intact but the somatic nerves severed.

The importance of the decerebrate preparation consists in the fact that from its study in the hands of Sherrington and others, most of the prevailing ideas of muscle tone are derived. Sherrington proved that the tone of skeletal muscle was postural in function. He found that the typical position of the decerebrate animal was that of "reflex standing," with all four limbs rigidly extended, and the neck retracted to a greater or lesser degree. Between these phases there were periods in which the limbs were no longer maintained in extension. During these periods, or when the extension of the limbs was overcome by passive movement, the musculature was found to exhibit a condition of "plasticity." If the leg were flexed at the knee, so lengthening the extensor muscle of the thigh this position was retained ("lengthening reaction"). If the knee were now extended, so shortening the extensor muscle the new position was again maintained ("shortening reaction"). Sherrington (*Brain*, 1915) called the property of skeletal muscle, which enabled it to exhibit these reactions, "plastic tone." He emphasized the fact that the degree to which this property was exhibited was independent

¹ Since published in *The Medical Journal of Australia*, January 10, 1925.

of the length of the muscle fibres exhibiting it. And very correctly, following the suggestion of Grützner and others, he compared this property of skeletal muscle to that of involuntary muscle, such as that of the bladder wall, which enables it to adjust itself to enclose an increasing volume under practically the same wall-tension. Speaking of this comparison Sherrington says: "Both are instances of the postural contraction of muscle; though the relation of the central nervous system to the postural activity is very different in the two cases." For Sherrington believed that the tone of striated muscle was entirely dependent on the intactness of the somatic motor nerve supply, while involuntary muscle can exhibit tone in the absence of its innervation.

The objection to the view that the tone of skeletal muscle is partially governed by the sympathetic nervous system on the ground of the inconsistent and negative results of experimentors employing the decerebrate preparation for investigating this problem disappears now that Royle's and my experiments and surgical operations have demonstrated the influence of the sympathetic. In this work evidence of the connexion of the sympathetic innervation with the tone of skeletal muscle is forthcoming not only from experiments upon the decerebrate goat but from the effect of sympathetic ramisection in patients suffering from forms of spastic paralysis, which, prior to operation revealed all the essential qualities of decerebrate rigidity. In normal, spinal, and decerebrate animals, and in human patients, sympathetic denervation of the limb musculature led to *a consistent qualitative alteration in muscle tone*. The defect was found to be a lessening of the efficiency of the muscle in maintaining a position once it had been assumed. This was the case whether the position had been imposed passively, reflexly, or by voluntary contraction, and as I have previously argued (*Brain*, 1924) is due to the same fundamental change namely, the loss of plastic tone. In the decerebrate preparation, after passive movement, the limb deprived of its sympathetic innervation failed to maintain the new position imposed upon it either when the extensor muscles were lengthened or shortened. Instead, the limb would fall back to a posture determined by the action of gravity and the length of the fibrous tissues composing it. This illustrates the effect of sympathetic denervation to remove plastic tone, as evidence of which is the absence of the "lengthening and shortening reactions" of Sherrington. The skeletal muscles of human patients show a similar qualitative alteration. This is clearly shown for instance, in one of Dr. Royle's patients with spastic paraplegia supervening upon a gunshot wound of the cortex. Prior to operation this patient clearly exhibited "lengthening and shortening reactions" of the extensor muscle of the knee. Before operation if the left thigh were lifted from the bed the unsupported leg would remain extended for a long period of time. If the extended leg were

passively flexed at the knee-joint it would remain flexed in its new position. If it were now passively extended the extended position would be maintained. After left lumbar sympathetic ramisection these reactions, which are identical with the "lengthening and shortening reactions" of the decerebrate preparation described by Sherrington were no longer exhibited, *i. e.*, plastic tone was removed by the operation.

But it is important to notice that tone does not entirely disappear after sympathetic denervation. Only one efferent pathway to the skeletal muscle has been removed. The remaining somatic innervation is responsible for another component of muscle tone. In the acute decerebrate preparation, for instance, notwithstanding the removal of its sympathetic nerve supply, the typical extensor attitude of the limb is assumed. The neuro-muscular mechanism concerned in imposing the extended position is obviously intact; *i. e.*, the medullated somatic nerves are responsible for this function. It will readily be seen that the extensor muscles must be shortened in order that the extensor attitude of the limb may be attained. The antagonistic muscle groups, on the other hand, are reflexly inhibited, as Sherrington's studies of the acute decerebrate preparation have shown. Their component of tone, which is somatic in origin, and is exhibited as a degree of contraction of selected muscle groups may, following Langelan, be called "contractile tone."

Contractile and plastic tone are both postural in function. Contractile tone imposes posture as a result of shortening of appropriate muscle groups; plastic tone takes part in maintaining this posture once it has been attained by fixing the length of the muscle exhibiting contractile tone. On account of the responsibility of these two components of tone in the production and maintenance of posture they may together be referred to as constituting postural tone.

As Sherrington's deafferented preparations show, the production of postural tone depends upon the existence of proprioceptive impulses. Posterior nerve root section in all the spinal segments connected with a given muscle removes both contractile and plastic tone. Impulses arising in the muscles, therefore, discharge through both the somatic motor nerve roots and the white rami of the sympathetic nervous system. In other words contractile tone is subserved by a somatic proprioceptive reflex arc; plastic tone is governed by a sympathetic and reflex arc. On account of the limited connexions of the sympathetic nervous system with the spinal cord, these reflex arcs for a given muscle group are usually situated at different levels of the central nervous axis. Purely spinal reflexes are, however, inadequate in higher vertebrates for the exhibition of the postural tone responsible for the natural attitudes of the body. The reflexes responsible for the extensor attitude of the lower extremities depend, for instance, upon reflex arcs which pass as

high as the pons in the brain stem. It appears that the vestibulospinal tract is the descending limb of the reflex arc subserving the contractile tone to the extensor muscles of the limb; while plastic tone depends upon a reflex arc the descending limb of which is constituted by the ponto-spinal tracts. I have recently argued that these reflex arcs are governed by the tectum, substantia nigra, and red nucleus of the midbrain, the corpus striatum, and the cerebral cortex by way of the cerebellum. The influence of all these structures upon postural tone is produced ultimately through both the somatic and sympathetic efferent connexions to skeletal muscles. In other words there are two final common pathways to such muscles. The excitatory impulses emerging through the somatic-motor pathway to provide muscle tone give rise to contraction of the muscle and contractile tone. The effect of the excitatory impulses emerging through the sympathetic rami communicantes is to fix the existing length of the muscle (plastic tone). It is obvious that this is a primary subdivision of postural tone according to the properties subserved by the two efferent connexions of skeletal muscle. The sources of the impulses emerging through each pathway are numerous in each case, as already mentioned. Both connexions are in fact final common pathways in the sense of the term employed by Sherrington.

III. Technique of Experiments in which the Decerebrate Animal was Employed to Determine the Effect of Removing the Sympathetic Innervation of Skeletal Muscle. The negative and inconsistent results obtained by previous investigators employing the decerebrate preparation to determine the function of the sympathetic innervation of skeletal muscle call for comment. The following points appear to have been of importance in leading to the success of the experiments of this kind in the hands of Dr. Royle.

1. *The Interval between Two Stages in the Operation.* In our earlier experiments the lumbar portion of the sympathetic trunk was removed from one hind limb in goats. This was done as a preliminary procedure. Then, at a variable period after this operation, decerebration was performed. In the first series the interval between the two operations varied from seven to seventy-three days. The best contrast between the hind limbs on the operated (left) and inoperated (right) side was seen in the animal in which the interval between the operations had been longest. In this animal extension of the left limb was easily overcome in contrast to the opposite limb. When not handled with the animal lying in the fixed supine position, the left limb rapidly fell from its temporary position of extension to a passive posture of semi-flexion. In this stage of relaxation the "lengthening and shortening reactions" were absent.

Kulchitsky has demonstrated (*Journal of Anatomy*, January, 1924, p. 160) that "the medullated and non-medullated fibres never

terminate in the same muscle fibre." In other words each voluntary muscle is formed partly of actively contractile fibres innervated by somatic nerves and partly of striated muscle fibres, which are not contractile (although their length may be altered passively by the contractile fibres). The latter are innervated by post-ganglionic sympathetic fibres and their activity is controlled by the sympathetic ganglia under the influence of the white rami communicantes of the thoracico-lumbar outflow from the spinal cord.

These three observations depend upon the loss of plastic tone. The comparative ease in performing passive flexions of the extended limb is due to the fact that contractile tone, which is responsible for thus imposing this position, alone has to be overcome, to alter the position. On the intact side while contractile tone is responsible for the position of extension it is assisted by plastic tone, which tends to fix the length of the muscles necessary to maintain this position. When contractile tone is overcome on the partially denervated side, no further resistance to movement is offered. On the opposite side though resistance suddenly gives way when reflex shortening of the extensor muscles (*i. e.*, contractile tone) is overcome, some degree of resistance to passive flexion is still maintained, which is to be attributed to the existence of plastic tone. As Walshe has pointed out this phenomenon has its counterpart in the clasp-knife effect of decerebrate rigidity.

Some decerebrate rigidity is due to the presence of an exaggerated degree of both contractile and plastic tone. The extended position imposed by contractile tone due to the selective reflex shortening of the extensor muscles is rigidly maintained by the fixation of the extensor muscles in their shortened state by plastic tone. In the absence of plastic tone this rigid fixation is no longer apparent and the limb fails to maintain the extended posture once the reflex shortening of the extensors (dependent upon impulses emerging through the intact medullated somatic nerves) ceases. The active posture of extension is now no longer maintained.

When the limb was passively extended or relaxed spontaneously, it would fall into a semi-flexed position determined by gravity and the length of the fibrous tissues contained within the limb. If the knee joint were now passively flexed or extended the leg would resume its original posture. In other words a passive posture characterized the limb instead of the ability to occupy active postures, which is the property of the normal musculature in the decerebrate preparation. For the "shortening" and "lengthening reactions" are no longer exhibited, *i. e.*, plastic tone is absent.

Unquestionably these three manifestations of the loss of plastic tone are not so clearly exhibited when the interval between lumbar sympathectomy and decerebration is short, *e. g.*, when decerebration is performed in the same day as that on which the lumbar

sympathetic trunk is removed. I have records of three decerebrate preparations which exhibited the "lengthening and shortening reactions" in this way when both procedures were carried out on the same day. In each of these however the resistance to passive flexion and the tendency for the maintenance of the extended position were definitely less than on the control side.

The explanation of the progressive loss of plastic tone may be that this property of skeletal muscle is less dependent upon impulses emerging from the central nervous system than is contractile tone. In this respect skeletal muscle would resemble, to a certain degree, smooth muscle, the tone of which is not absolutely dependent upon its nerve supply. There are difficulties in supporting this analogy, because recovery in the tone of involuntary muscle following denervation of involuntary muscle occurs as time advances. But in view of the fact that only some muscle fibres receive sympathetic nerve fibres and are therefore alone responsible for the property of plastic tone, it is feasible that these denervated "fixing" fibres slowly lose this property after sympathetic denervation, so differing from the neighbouring "movement" fibres, which are absolutely dependent for their property of contractile tone upon the intactness of the central connexions of the somatic nerve fibres that supply them. Moreover in the lumbar operation, so far employed, it is necessary to bear in mind that all the sympathetic ganglia from which the gray rami to the lower limb arise are not removed though efferent impulses to them from the spinal cord are not removed. This fact may, in some measure, perhaps account for the progressive loss of plastic tone. The entire question, however, of the determination of the time necessary to produce the complete effect after sympathetic denervation is under examination. It can best be settled by studying the effects of the operation in the chronic decerebrate animal described by Bazett and Penfield. The introduction of the interval operation disposes of certain statements which have been made previously to explain the changes seen following sympathetic denervation. In the first instance diminution in tone cannot be ascribed to sensory inhibition due to the wound inflicted in performing the operation of sympathectomy. For, ample time is provided to allow healing of the wound to occur. Nor are the changes due to vasodilatation because the diminution in tone permits, or even increases in degree, although the vasomotor changes are a maximum immediately after the operation (*cf.* Bayliss, Hartman, Blatz and Kilborn). Sympathetic ramisection in human patients affords similar results in this direction: for the loss of plasticity has persisted for twelve months in the case of the first patient subjected to operation, although obvious vasomotor changes were only present in the first few weeks (Royle). In other patients the circulatory disturbance has been of greater duration but it had a general ten-

dency to be reduced in degree though the loss of plastic tone was still apparent. Some of the effects upon tone of sympathetic ramisection may, however, be due to the attendant increase of blood supply to the limb. I refer to its effect upon contractile tone. Dr. Royle has noticed, for instance, that cold has less effect in increasing contractile tone in the limb of a spastic paraplegic which has been subjected to operation than in the limb of the opposite side. As the result of vasoconstriction the limbs of the spastic paralytic are invariably colder than normal. The advent of vasodilatation with an attendant increase in temperature of the limb lessens the degree of contractile tone. This reduction is greater immediately after the operation than it is subsequently: for the vasomotor changes become less marked as time proceeds. But the reduction in plastic tone progresses in the opposite direction.

2. *The Method of Examination of the Animal.* After removal of the sympathetic innervation of one limb the otherwise intact goat can walk, and run, in the normal manner. The characteristic change produced by the operation is revealed, however, if the animal is placed in the supine position with its head held rigidly in the midline. All limbs take up an extended posture under these conditions, but as Dr. Royle has shown, when all cause for alarm is removed by gentle handling of the animal, the lower limb of the operated side falls from the extended position into a passive posture determined by mechanical factors. This method of examination for changes in the postural tone of the limb was adopted with advantage for the decerebrate preparation. The goat is placed in the supine position in a cradle and the head is held firmly in the median line or the animal is first encased in a leather jacket which fits round the trunk and neck and then placed in the cradle. In this way the effects of the tonic labyrinthine and neck reflexes of Magnus and de Kleijn are excluded. Under these conditions the typical extensor posture, as already explained, is assumed by all four limbs. But after a short period the limb which has been deprived of its sympathetic innervation falls under the action of gravity to a passive posture of abduction and semi-flexion.

By this method of examination any defect in the maintenance of posture is readily indicated by failure of the skeletal musculature to support the weight of the limb. This is a matter of importance: for efforts to test for diminution of tone by passive movement set up a reflex spasm of the musculature of the limb, which is evidence of the excitability of the nervous connexions responsible for contractile tonus. Clinicians are familiar with this observation, for spastic muscles may before palpation show no evidence of an increased degree of contraction, but a reflex tonic contraction is set up immediately passive movement is attempted. In the first phase the posture is maintained predominantly by plastic tone. After

examination of the limb is commenced increased contractile tone is superadded. Obviously the effect of passive movement will be to obscure any diminution in the degree of plastic tone.

Nevertheless passive movement overcomes contractile tone alone more easily than contractile and plastic tone combined, as has already been discussed.

3. *Avoidance of the Effects of Asphyxia and of Anemia of the Brain Stem.* It is clear from the foregoing argument that the results of loss of plastic tone would be more difficult to observe if any condition existed which would unduly increase the degree of contractile tone. As Dr. Royle (*The Medical Journal of Australia*, September 27, 1924, p. 315) has pointed out, asphyxia of the animal would produce this effect. To avoid this complication he employed intratracheal anesthesia and then oxygenated the animal freely as soon as decerebration was performed. If asphyxia tended to develop later, *e. g.*, when the tube in the trachea was too small, the rigidity in extension of all four limbs would become extremely marked and differences in the tone of the hind limbs (due to the loss of plastic tone on one side) would be markedly obscured. Removal of the cause of asphyxia would invariably remove the tendency for the display of such an exaggerated degree of contractile tone. In recent papers Walshe has argued from physiological evidence, that minimal degrees of oxygen in like manner may lead to hyperexcitability of reflex arcs. Evidence is accumulating that this factor may account for so-called "irritative" symptoms following central nervous lesions. But the effects of asphyxia and anemia, which are manifested as reflex hyperexcitability, are foreign to the condition of tone decerebrate rigidity. Like the state of spastic paralysis this condition is to be regarded as being due to a release of function in the nervous system, following the removal of higher levels of nervous activity. The term release is employed in the sense advocated by Hughlings Jackson, and developed in the present century by the work of Head and his collaborators. For this reason it appears to me that the Sherrington method of decerebration, which should be carried in the goat by section of the midbrain under direct vision, is preferable, for the purpose of observing the presence or absence of plasticity, to the method of decerebration by anemia induced by combined ligation of the carotids and basilar arteries which has been introduced by Pollak and Davis. While such a preparation is unquestionably most useful for observing the reflex activities of such an animal, it is impossible to be certain in how great an area of the brain stem the cell stations are hyperexcitable due to the presence of a degree of anemia which is insufficient to abolish function altogether.

4. *The Choice of Laboratory Animal.* The animal selected for the operations, in the first instance, was the rabbit. Dr. Royle

procured an excellent result, consisting in the diminution in tone of the hind limb of a spinal rabbit on the side from which the lumbar sympathetic trunk had been removed. This effect was not reproduced in subsequent experiments and this failure was attributed to the difficulty in this animal of completely excising the sympathetic trunk on the selected side without injury or removal of the trunk of the opposite side. Therefore the goat, which had already been studied by us in connexion with the problem of determining the factors responsible for the symptomatology of complete transverse lesions of the spinal medulla, was employed in subsequent mammalian experiments. In this animal the lumbar sympathetic trunk is large, well defined, and easily traceable from the upper lumbar region to the level of the common iliac artery. It is separated from its fellow of the opposite side by a wide interval. In this way Dr. Royle's experiments, upon the effect of removal the sympathetic trunk on decerebrate rigidity, came to be performed on an animal with simple postural reflex activities of the limb musculature. "Reflex standing" is beautifully illustrated in the well oxygenated decerebrate goat. This is especially true of the hind limbs in which the degree of rigidity is invariably as great, or may be greater than in the fore limbs. With the goat in the fixed supine position loss of plastic tone becomes apparent by early failure in the maintenance of the extended posture of the defective limb. This observation was identical with that already made on such an animal prior to decerebration. In contrast to the goat, a carnivorous animal such as the cat shows a capacity for great variation in the degree of postural tone. The cat does not take up the extensor posture, when placed in the supine position. Variation in the degree of contractile tone in its four limbs impose varied attitudes upon it, and no doubt in the well oxygenated decerebrate cat the variations in the degree of rigidity of the limbs which are encountered are to be accounted for in a like manner. Such variations in the degree and selective activity of contractile tone possibly make the effects of loss of plastic tone less apparent than would otherwise be the case and render an analysis of the exact defect in tone more difficult at the outset. For it must be borne in mind, in this connexion, that in the experiments recorded in the literature, all of which were performed on cats, differences in the degree of tone upon the two sides follow unilateral sympathectomy, which was performed in some cases before and in others after, decerebration. For instance Dusser de Barenne observed a diminution in tone in five cases out of nine, after midlateral removal of the lumbar sympathetic chain. Uyeno found differences in the tone of the fore limbs after removal of the ganglion stellatum on one side, but attributed the diminution in tone to sensory inhibition due to the wound on this side. In Royle's experiments this explanation is not admissible. Consequently the problem present-

ing itself is not to explain negative results but inconsistent results. I believe that the factors to which attention has been called in the foregoing discussion explain the failures encountered. This is especially the case when it is recognized that investigators in the past have been seeking to observe quantitative diminution of tone. I have attempted to show that contractile tone is well displayed after sympathetic denervation and under certain experimental conditions may be present in an enormously exaggerated degree. It is only when qualitative changes due to the selective removal of plastic tone are looked for that the interpretation of effects in any such instance becomes clear.

The thesis maintained in this paper that plastic tone is a property of the sympathetic innervation of skeletal muscle no longer rests upon the evidence provided by experimental decerebrate rigidity. For the same effect as that which follows sympathetic denervation in the decerebrate animal is produced by sympathetic ramisection in men in those conditions of spastic paralysis and the extended form of paraplegia, which exhibit all the essential qualities of decerebrate rigidity. The excessive plastic tone characterizing these conditions is removed by the operation. The evidence of this fact which may be obtained by studying the character of the knee jerk is of special interest. For in both decerebrate rigidity and in the types of spastic paralysis to which reference has been made, the slowness in execution of the knee jerks became brisk in character. This is due to the rapid rate of relaxation of the extensor muscle after completion of the jerk contraction which replaces the former tendency of the muscle to remain shortened ("shortening reaction") when contraction ceases.

Further the evidence adduced by Langelaan, as the result of his work on frogs, is in favor of the view that plastic tone of skeletal muscle is subserved by its sympathetic innervation. I have been able to confirm Langelaan's observations by a series of experiments on the influence of the double innervation upon the posture of the wing of birds. These experiments include the unmasking of plastic tone by removing the somatic innervation, subsequently rendering the plastic wing flaccid by removal of the influence upon it of the cervical sympathetic trunk. But this paper has been confined to a discussion of the effect of sympathetic denervation upon the muscle tone of the decerebrate preparation. The reason for this is that most of the scepticism in regard to the validity of any theory which relates the sympathetic innervation to the tone of skeletal muscle, has been aroused in the past by the failure of various workers to modify consistently the onset or development of decerebrate rigidity by sympathectomy.

SOME NOTES ON CANCER.

II.

ON HUMAN INTESTINAL PARASITES AS A CANCER INCITING FACTOR
AND ON THE SIGNIFICANCE OF THE PRECANCEROUS STATE.*

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ON basis of extensive studies of the literature on cancer the writer, in a previous paper (I),¹ emphasized the utter improbability of the existence of a specific causative cancer microorganism. He endorsed the opinion of those who consider it no longer tenable to have an open mind with regard to that question. With them he took the stand that where cancer appears to be due to the action of bacilli, it arises, as in other cases, from chronic irritation, in this case from the irritation emanating from the bacilli. Continued study of the literature has only deepened that conviction.

It may not be inappropriate, once more briefly to point out the difference in the attitude to cancer genesis of the adherents of the specific theory and of those of the nonspecific theory, making use for this purpose of certain work of Yamagiwa.² That author said (1905) at the end of a set of theses: "There is no specific microorganism of cancer." A few years later, when Fibiger, by means of a nonspecific worm, had produced the first experimental primary carcinoma, Yamagiwa felt stimulated by that great success into attempting to prove his thesis by other nonspecific means and, together with Ichikawa, produced the first experimental primary tar carcinoma (1913).

In these experiments, on removal every third or fourth day of the previous tar application before putting on the new coat, not infrequently bits of epidermis would be torn off with the hardened tar crust, causing slight hemorrhages. The nonspecificists consider such lesions as rather inconsequential. But the specificists—and there are those whose opinion commands attention—see in them the gate for the entrance of the alleged ubiquitous specific cancer parasite into the system of the animal that is being tarred. They deny the contention of the nonspecificists that long-continued irritation of tissue by means of a nonspecific substance is of itself, and exclusively, responsible for the observed experimental result, that is, the primary carcinoma at the point of application of the irritant, and claim that not the irritant, but the presence of the

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about-to-be-discovered specific agent is the cause of the observed cancerous process.

"Admissible in medicine," says Orth,³ "is any hypothesis and theory competent to give a satisfying explanation of verified observations; but no hypothesis and no theory that lays claim to consideration can afford to disregard established facts." It appears proper then to inquire, how by means of the specific theory the case of Niebergall,⁴ for instance, can be explained, in which myomata, polypi, sarcoma and carcinoma were found in the same uterus, or the case of Petersen,⁴ who found a tumor having grown expansively (*i. e.*, benign fashion) into the depth and progressively (*i. e.*, malignant fashion) in a lateral direction.

The concomitant of the cancer bacillus is, of course, the cancer serum. From Adamkiiewicz's cancroin, thirty years ago, down to our day serum after serum has been brought out, every one of them prepared from an isolated alleged specific cancer microörganism. Just now there seems to be a recrudescence of such efforts. However, even a successful cancer serum would prove nothing for the specific theory. It would merely be another instance of the well-known fact that injected foreign protein may make more or less impression on diseased tissue. But in order to do that the protein does not have to be of bacterial origin, nor must the diseased tissue necessarily be cancerous. The possibility that injection of foreign protein into a cancer patient should occasionally create the illusion, temporarily at least, of a complete recession of the tumor, is freely conceded; but the result cannot be repeated at will; it just accidentally happens. Moreover, such retrogression has dangers; the serum is apt to destroy the cancer cells so quickly and thus flood the system with the decomposition products of cancer cells in such quantity, that the system cannot cope with this poison, and the patient dies from getting better. Proper dosage might perhaps be found if all cancers were alike; but they are all different, and consequently, at best, a serum treatment in cancer, by its very nature, must, as regards dosage, always remain guess work. So from whatever point of view we look at the effort to find a specific cancer microörganism, it appears to be an endeavor leading in all probability nowhere, even if successful.

For these and other previously expressed reasons¹ the writer has joined the ranks of those cancer students who have definitely written "finis" under the "specific" chapter of cancer etiology. But not satisfied with assuming a purely negative stand, the writer is trying to obtain insight into the genesis of cancer by plodding in the cancer literature, carrying together therefrom mutually supporting experimental results, observations and deductions, analyzing them and arranging them in logical sequence, with the idea in mind of focussing the consensus of opinion and of getting at the trend of it.

In my first communication on cancer,¹ nonspecific parasites came

in for more or less attention. Inasmuch as all the numerous, though otherwise unrelated cancer-inciting factors lead up to the same result, namely cancer, it appeared of no particular consequence which one of them should be selected for more detailed study. It was, therefore, thought best to continue with the parasites.

The human intestinal parasites, helminths,⁵ so far as medicine is interested in them from the point of view of cancer, are various nematodes, trematodes and cestodes. The life histories of these parasites have certain features in common:

1. They all have no less than three stages of development, ovum, larva, worm; and (excepting only *Trichinella spiralis*, the larvæ of which are born alive, without the preceding deposition of an ovum) they come in contact with man in all three stages. Those of the parasites in question which have more than three stages of development, go through the additional stages in intermediate hosts, molluscs and fishes, but come in contact with man also only in the same three stages, as do those which have but three.

2. All the parasites in question, at certain periods of their evolution, require a complete change of nutritional environment for the attainment of the next stage of their development, that is, they require a change of hosts or they require a temporary life in the open air or in water and subsequent return into a host.

3. In the larval stage all the parasites in question migrate more or less extensively within the human body, quite a number of them following a certain typical route: from the intestine to the lungs, to the pharynx and back to the intestine, and only by the performance of this circuit can those asexual larvæ develop into sexual worms.

4. All these parasites, as stated in my first communication,¹ are organotrope, that is to say, they exhibit an apparent predilection for one organ or another, and in that organ they make their habitat. The reason for this phenomenon is undoubtedly the fact that they find there the medium best suited to their nutritional requirements and the conditions which, in respect of their anatomical peculiarities, facilitate the satisfaction of these requirements. What enables a special parasite to link up with a special organ remains unexplained, unless the assumption be accepted as an explanation that the parasites swarm all over, but that only those survive which reach the suitable environment.

On reflection, the feature around which best to group the proposed discussion appeared to be this fact that all these parasites come in contact with man as ova, as larvæ and as worms, as all three stages, in one or the other of the parasites, have been found to enter into the causation of precancerous conditions.

Ova as a Cancer-inciting Factor.—Ripe ova of ascaris (Küchenmeister, *et al.*⁶) and the embryos of tapeworms (Braun, p. 250⁵) have

been demonstrated (Shinohara⁷) on garden fruit and green vegetables. Against eating such raw food Metchnikoff⁸ warned from the point of view of danger of infection with parasites. Borrel,⁹ in 1908, repeated that warning from the point of view of cancer, and again in 1923, a warning in which the International Cancer Congress held at Strassbourg concurred by general resolution.

Under normal conditions the smooth ova of roundworms (nematodes) and tapeworms (cestodes), as ordinarily deposited in the lumen of the intestine, are harmless; but it will be seen below that in cases where ascaris worms (nematodes) or adult liver flukes (trematodes) force an entrance into the liver or gall bladder or pancreas, the ova there deposited by them contribute their share toward the injurious consequences of such invasion.

Harmful of themselves, on the other hand, are the spiked ova of the Bilharzia parasites (trematodes).¹⁰ These worms live in the portal venous system, and their ova are normally deposited in the capillaries of the pelvic venous plexuses, vesical, rectal and genital. Only a small part of the total number of ova so deposited reach the evacuating channels; billions are left behind in the tissue, die there and are calcified (Lortet and Vialeton, pp. 12, 60, 96¹⁰) so that the infested tissue becomes completely saturated with innumerable minute pointed particles of lime or chalk, an ever-present source of severe irritation. On section such tissue creaks under the knife (Chaker, p. 33¹⁰).

Infestation with Bilharzia takes place in the larval stage of the parasites, the larvæ entering through the skin or mucous membranes when these organs come in touch, through drinking, bathing or walking barefoot on wet ground, with water contaminated with the larvæ. Among town dwellers, with little or no chance of reinfection, the majority of cases rarely get beyond the first symptom of bilharziosis: hematuria (Milton¹⁰), which is so common in Egypt as to be almost universal and to be scarcely considered abnormal.¹¹ But among the rural population (fellahs), whose work with bare arms and bare limbs in the irrigated fields and irrigation ditches of the lower Nile Valley exposes them to frequent reinfection, the ravages of the disease for which no real remedy is known, are appalling. In these severe cases the disease takes the form of papillomatous degeneration of the mucous membrane of the bladder, or of the bowels including the rectum, and of polypous growths arising from the submucosa (Küchenmeister, *et al.*),¹² which necrose, separate at their pedicles and result in ulcerations of dysenteric appearance.¹³ So also does bilharziosis of the glans penis give rise to ulcerations.¹⁴ All these ulcerations are caused by the chronic irritation of the tissue arising from the calcified ova. They are chronic, nonhealing lesions; as such they are a precancerous state. In course of time a certain percentage of such lesions become definitely cancerous.

Very large accumulations of Bilharzia ova have also been found in

the seminal vesicles and in the glands and organs contributory thereto (Chaker, pp. 36, 37¹⁰) and have been demonstrated in the ejaculated sperma (Lortet and Vialeton p. 14¹⁰), an occurrence to which the term ovispermia has been applied.¹⁵ It is a fair presumption that ova from that source may find lodgment in the mucous membrane of the vagina, adhering thereto with their spikes. A male bilharziosis patient who was positively not reinfected and was kept under constant medical supervision as many as ten consecutive years, at the end of that period still discharged daily, undiminished quantities of ova (Lortet and Vialeton, pp. 14, 16, 17¹⁰). Not unlikely, therefore, in a long married life, the husband having bilharziosis, Bilharzia ova may accumulate in the vagina of the previously healthy wife in quantity sufficient to induce therein primary lesions of the severity of those seen in the bladder and in the rectum of the fellahs. This may occur in a woman whose cervix uteri, bladder and rectum are perfectly healthy—proof that the ova did not come from within, but came from without. There is a case on record where such a history of the growths found in the vagina was strongly suspected (Madden).¹⁶ But the occurrence is probably not as infrequent as the fact of there being—as far as I was able to find—only one such case reported, and that incomplete, would seem to suggest. Young Egyptian boys are proud when seized with hematuria, considering it a sign of attained manhood. Without reinfection the hematuria which they can see subsides in the course of years, but the nonvisible ovispermia remains as a danger for their prospective wives. The women of the agricultural population of Egypt never see a doctor, and the men do so only when they “drop in their tracks.” As it is just in this class of people that conditions such as stated would be most likely to occur more often, scarcity of observation cannot be considered as reflecting on the likelihood of the occurrence (Milton, Madden, Lortet and Vialeton,¹⁰).

There would then have been found here a strong probability of a real “cancer à deux,” not that fabled one of the alleged transfer in married couples of cancer cells or of an imaginary specific cancer microörganism from one partner to the other; but the actual transfer per coitum of a nonspecific cancer-inciting factor, namely, spiked calcified ova, from the Bilharzia infested husband to the previously uninfested wife, with the prospect of a primary vaginal cancer in the wife.

There are, of course, numbers of women in Egypt and elsewhere who contract bilharziosis the same as do the men, by primary infestation, especially the fellah women who are assisting in the work in the fields. In them bilharziosis of the vagina is said to be very frequent and to take the form of an acute vaginitis (Fantham, p. 643⁵).

Common in such cases is also the involvement of all parts of the

vulva in the bilharzic process, principally of the labia minora, where warty masses are seen; shaped like bunches of currants and comparable to condylomata acuminata (Koch, p. 55⁸). There occur in them also polypoid tumors in the cervix uteri. One such, the size of a hen's egg, reported from Mauritius, on being excised, creaked under the knife and, on microscopical examination, was found to consist of dense strands of fibrous tissue enclosing Bilharzia ova. "The diagnosis of the origin of these growths, so common here in Mauritius," says the author, "leads one to expect that many similar cases are to be found in other tropical countries where bilharzia disease is common."¹⁷

American interest in bilharziosis is not so far removed as it would seem to be on first impression. Considering the heavy tourist travel to Egypt and contiguous countries, the possibility of visitors acquiring bilharziosis is a matter of rather considerable actuality. Most all open water courses, lakes, ponds and pools near human habitations in Africa and in the contiguous southerly parts of Asia Minor contain Bilharzia larvæ. The same as in the case of hook-worm larvæ (p. 67¹⁸), the mere touching of the skin with gloves or socks wetted with Bilharzia-contaminated water is probably sufficient for infestation to take place. During the World War many of the soldiers from Australia and India, quartered in Egypt, fell victims to bilharziosis for which, as stated, there is no known remedy,* and the question of how to handle them after they returned home, to prevent the importation of the disease into previously clean districts, became quite a problem. The two danger points are: (1) The discharge of ova with the feces or urine of Bilharzia patients into or near fresh water; (2) the presence in the water of suitable molluscs. Where the latter are wanting there is no danger of the spread of the disease (Manson, p. 63¹⁰).

Summary of Section on Ova. 1. Precancerous lesions, nonhealing superficial ulcerations, are produced by the spiked ova of the Bilharzia parasites in the bladder, the bowels, the rectum and the genitals.

2. Bilharzia ova have been demonstrated in the ejaculated human sperma ("ovispermia").

3. Ova having a smooth surface can become a contributory factor in the production of precancerous lesions, as for example, when liver flukes and ascaris worms deposit ova in the gall bladder and in the bile ducts of the liver, or in the ducts of the pancreas.

Larvæ as a Cancer-inciting Factor.—Mention was made above of the typical migration in the human system of the larvæ of some of these parasites over a well-defined circuit, from the intestines by various routes to the lungs, thence to the pharynx and back to the intestines.

* Recent reports announce promising results of tartarus stibiatus, given intravenously.

In this connection an interesting phenomenon has been observed in the migration of hookworm larvæ through lymph glands, especially the inguinal and axillary glands. The larvæ arrive there performing the characteristic larval wiggling motion by which they force their way through the cell masses. After a while the pace of some of them is retarded, owing to lymph cells attaching themselves firmly to their surface. For a while the larvæ drag the load along, but eventually, though still wiggling, make no more headway; soon the wiggling also ceases and the result is an asphyxiated larva, lying dead in the gland, buried in a thick envelope of lymph cells.¹⁸ The same fate has been observed to overtake ascaris larvæ in the pleural sac.¹⁹ Such captured larvæ then undergo necrobiosis with consequences similar to those discussed further down with reference to worm nodules.

As regards the lesions in tissues and organs owing to their penetration by migrating larvæ, light has been sought thereon by experiment.

1. "On flooding a young pig with ascaris larvæ, both lungs were found greatly swollen, edematous, intensely hemorrhagic, the color of liver, and extensively hepatized. Microscopically the pathological picture varied from that of an acute lobular pneumonia in which the areas of inflammation centered around the bronchioles, to lobar pneumonia in the stage of red hepatization. A photomicrograph showed areas of consolidation, the alveoli being almost entirely filled with serosanguinolent exudate, also extensive immigration of leukocytes and the round-cell infiltration characteristic of acute inflammation, and, in other portions, enlarged alveoli, indicating a compensatory emphysema" (p. 22²⁰).

2. On flooding the system of a young guinea pig with hookworm larvæ, one lung became "solidified with blood and the other contained numerous larger and smaller hemorrhagic spots" (Dock and Bass²¹). Mechanical injury could not have caused the latter, because ecchymoses have been observed in such cases in the axillary and inguinal glands prior to the arrival of the larvæ therein; the ecchymoses rather appear to be due to the concentration in the system of toxins from the mere massive invasion of hookworm larvæ (Looss, p. 53¹⁸).

3. In a similar experiment the liver was found diffusely affected, not only with such hemorrhages, but also with necrotic spots; in the immediate neighborhood of the latter were observed hypertrophic liver cells and numerous mitotic cell divisions, while at some distance from the same were located a great many round, well-defined tissue infiltrations, consisting mostly of leukocytes and, in many instances, containing larvæ.²¹

As regards the bearing of the foregoing observations on human conditions, flooding of the human system with ascaris larvæ is not a likely occurrence, because for every ascaris larva migrating therein,

a ripe ascaris ovum must first have been ingested, and that does not usually happen in quantities.

The same applies to the embryo of the tapeworm (Braun, p. 250⁵), of which ordinarily one or a few are ingested at a time. Occasionally however, the position of the tapeworm in the intestine may become reversed and in vomiting,²¹ especially during pregnancy (Küchenmeister, p. 13⁵), ova-carrying links of the worm are then apt to get lodged in the stomach. In that event hundreds and thousands of ova will be set free in the stomach at the same time, flooding the system with tapeworm embryos which then develop therein into cysticerci, that is, larvæ (Frangenheim, p. 464²¹).

Mass infestation of the human system is also a possibility in the instance of hookworm larvæ and Bilharzia larvæ, both of which invade the host through the skin. In the extreme case of such mass invasion, the lesions due to the migration of the larvæ may have cancerous potentialities, as indicated by the third experiment.

As a rule, however, in the human being, the lesions resulting from this on first impression so formidable looking phenomenon, that is, the migration of the larvæ, will hardly ever be sufficiently severe, or sufficiently lasting, to assume precancerous characters.

Encapsulated Larvæ. In contradistinction to the migrating larva the resting encapsulated larva appears to be frequently the inciting factor of cancerous developments. Light has been thrown on this matter by experiments on frogs which were infected with nematodes.²² The migration of larvæ was here experimentally produced in the frogs, and the day-to-day progress of the induced phenomena of migration and encapsulation was established by a series of 85,000 sections. The processes set up in these capsules in frogs are not generally recognized as actually malignant.²³ Did the critics perhaps overlook the fact that metastases were formed (Kopsch, p. 115²²)?

Even more monumental is a long line of experiments on the conditions surrounding the encapsulated *Cysticercus fasciolaris* in rats (Bullock and Curtis).²⁴ In these researches the number of primary sarcomata experimentally produced exceeded 1000 in September, 1924.

These two so widely differing investigations seem to agree in a number of observations and deductions, which are: (1) That of several adjoining capsules only one may become cancerous; (2) that the point of origin of the active process is in the connective-tissue envelope of the capsule; (3) that at the beginning of the process only a small part of the envelope is involved; (4) that the onset of invasive growth appears to be conditioned on the presence of the live larva.

The reasons advanced for this latter assumption (point 4) are in the instance of the larval nodules in frogs the observation that nodules containing dead larvæ, as also nodules abandoned by the

larvæ after they had formed around them, did not become malignant, and that only those nodules showed invasive proliferation which contained a live larva (Kopsch, pp. 58, 114, 117²²).

In the case of the cysticercus cysts in rats²⁴ the condition of the larvæ in cysts which had assumed malignant properties seemed to depend upon the state of preservation of the cyst wall. "When the cyst wall was partly uninvolved by the tumor, or consisted largely of healthy tumor tissue, the parasite was alive and intact, but when the transformed cyst wall was involved in the tumor-necrosis, the larva was usually dead and distorted and even necrotic and fragmented."

From this observation the investigators made the deduction "that the live larva probably initiates the malignant process and that the death of the worm is secondary to the growth and necrosis of the tumor" (Bullock and Curtis, 1920, p. 169; 1924, p. 477²⁴).

The onset of malignancy in a capsule Bullock and Curtis ascribe to "some influence as yet undetermined" (1920, p. 156²⁴); Kopsch (p. 117²²) suggests "secretions and excretions of the larva," Fibiger,²⁵ in the case of the experimental spiroptera carcinoma of the rat, "a toxin emanating from the worm."

With reference to the deduction that without the influences emanating from a live parasite the onset of invasive proliferation cannot take place, it may not be amiss to call again attention to facts mentioned in part in my first communication,¹ namely, the finding of lifeless objects at the center of cancerous growths, objects which with equal justification as the live parasites, it would seem, can be considered bound up with the initiation of those growths. The cases referred to are: A completely calcified cysticercus surrounded by an infiltrating glioma the size of an apple;²⁶ a sequestrum of the radius in a fibrochondrosarcoma thirteen years after a compound fracture of the forearm;²⁷ in two instances, needles at the center of malignant growths;²⁸ in another instance a thorn;²⁹ the occurrence of melanosarcoma in the sole of the foot of African negroes through trauma from walking through thorny brambles;³⁰ the experimental production in rats of primary carcinoma of the tongue by means of bristles,³¹ and finally a piece of glass free in the peritoneal cavity of a mouse, which, failing to pass the pylorus, had caused there the onset of true cancer and eventually had cut its way through.³² Quite likely the chronic irritation produced by these inanimate substances was the inciting factor of the precancerous state from which developed the malignancy found surrounding them. If toxins were at work in the initiation of these invasive growths, as perhaps they were, the toxins in these cases certainly did not emanate from the inanimate inciting factor. Inasmuch as apparently the result of the effect arising from foreign inanimate as well as from foreign animate matter was the same, namely, malignant growth, it must be assumed

that both types of matter stand in a similar relation toward that growth, and that consequently parasites like inanimate factors, are not the direct cause of cancer, but the indirect cause of it, preparing the soil for it as it were; in other words, that these live parasites are also merely a cancer inciting factor, the initiators not of cancer, but of a precancerous state.

Summary of Section on Larvæ. 1. As a rule the lesions due to the migration of larvæ in the system appear neither sufficiently severe nor sufficiently lasting to cause the onset of a precancerous state.

2. In cases of frequently repeated massive larval invasion through the skin (hookworm, Bilharzia), or in cases of massive autoinfection (tapeworm), the migration of the larvæ may cause lesions having cancerous potentialities.

3. In contradistinction to the fact that migrating larvæ only exceptionally start the train of events ending in cancer, the resting, encapsulated larvæ are commonly found capable of becoming the inciting factor of precancerous conditions.

4. Whenever in such cases the precancerous state proceeded to definite malignancy the point of departure of the malignant process was found located in a small part of the connective-tissue envelope of the capsule of a live larva.

5. Inasmuch as dead matter, as well as a live larva, appears capable of inciting cancer the toxins emanating from the parasite probably merely cause the onset of a precancerous state, in other words, encapsulated larvæ would seem to be not the direct cause of cancer, but to be only of the dignity of a cancer-inciting factor. (See "General Summary" at end of article.)

Worms as a Cancer-inciting Factor.—Adult worms, ascaris and liver flukes, like larvæ, are frequently found to cause the formation of nodules in man; but the conditions surrounding the two cases are entirely different. While larval capsules and nodules as a rule enclose only 1, or at most 2 or 3 larvæ in the same capsule, worm nodules contain a great mass of worms as well as their ova and these ova, being smooth and consequently not capable of passive motion through the tissue, as are the spiked Bilharzia ova, stay where deposited (Koch, p. 59⁵).

An instructive instance of this kind is found in cases of long standing invasion of the liver with *Distomum hepaticum* in cattle (Küchenmeister, p. 99, ff³³). These liver flukes crowd into a bile duct as long as there is room for one more, blocking the lumen. The bile stagnates and decomposes and becomes sticky or hardens around the worms and the ova deposited by them. The pressure of this solid mass, its effect as a foreign body and the necrobiotic toxins emanating therefrom, affect the mucous membrane of the duct, change it to a tendon-like consistency and turn the duct into a rigid tube. Eventually inflammatory processes set in, and when,

as frequently happens, the worms have invaded a blind duct, the entrance to the same is apt to be closed behind them by the proliferating tissue, making the worms captives. Such foci in the liver are seen to develop in time into hard nodes, the size of a nut, which can be palpated from the surface. Cattle are ordinarily killed before the development of the precancerous state, presented in the nodes, can have run its course, but there is nothing to interfere with the completion of the process when worms invade the liver, the gall bladder or the pancreas of the human being and create conditions therein similar to those described for cattle. Such was the case with some of the eaters of raw fish mentioned in the first communication,¹ who therewith ingested the larvæ of *Opisthorchis felineus*, a liver fluke. Upon reaching the human intestine these larvæ develop into worms and then invade the common bile duct and the ducts of the organs resorting thereto, the total number of worms in the various ducts in some cases running up into thousands. Surrounding the worms the lumen of the ducts was found filled with epithelial detritus, leukocytes and the ova deposited by the worms. These worm nodules in the liver of human beings have in several instances been the point of departure of primary gelatinous carcinoma (Rindfleisch,³⁴ Askanazy³⁵). There were numerous metastases in the liver and in the epigastric lymph nodes (Rindfleisch 1910, p. 18³⁴). The unusual parasite and the unusual type of tumor were advanced as the reason for connecting both as cause and effect. There were besides other indications that such was the case. The malignancy was here apparently due to the toxins proceeding from the necrobiosis of the worms and of that of the cellular detritus.

Ascaris worms, like liver flukes have a propensity for forcing their way into narrow channels. In the feces of an insane person who had the habit of swallowing small glass beads, adult *ascaris* worms were found wedged in the holes of the beads (Mosler and Peiper, p. 313⁵; Fantham, p. 687⁵). In two other cases *ascaris* worms were found with marks of strangulation on their bodies, their discharge under anthelmintic treatment having cured a jaundice of long standing (Koch, pp. 119, 120;⁵ Fantham, pp. 688-689⁵). Direct proof of the invasion of the common bile duct and dependent organs by *ascaris* worms, was furnished by a series of observations made in the autopsy room in Manila (Crowell³⁶). In the tropics *ascaris* worms are looked upon by medical men "with respect and fear." "Migration of the *ascaris* into the common bile duct and thence into the gall bladder or into the intrahepatic bile ducts is a frequent occurrence and must be much more frequent than is indicated by the reported cases, as the diagnosis is made only at operation or at autopsy." . . . "After the death of the worms in the bile duct they become macerated or flattened, stained with bile, and may become incrustated with bile pigments" . . . "Worms may pass into the duct of Wirsung and determine either

the formation of abscesses or the development of an acute hemorrhagic pancreatitis. It also seems probable that the ascaris in the common bile duct may so block it as to lead to the development of an acute hemorrhagic pancreatitis without the entrance of the worm into the duct of Wirsung" (Crowell,³⁶ Mosler and Peiper, p. 313⁵).

The common bile duct and the duct of Wirsung are both too narrow to admit of the passage of full-grown ascaris worms. In passing, note should perhaps be made of the fact that the full-grown ascaris worm is as large in an infant as it is in an old man seventy years of age.³⁷ Full-grown ascaris worms found in the liver, the gall bladder or the pancreas can, however, under no circumstances have developed therein from either ova or larvæ, as sometimes suggested by authors, but must have invaded the organs from the intestine as worms, because ascaris ova mature nowhere else but in the open air, and ascaris larvæ cannot become worms until they have migrated over the above-described circuit which ends in the small intestine. The invasion of the biliary system and of the pancreas by these parasites must therefore be taking place soon after the end of the larval migration, while the ascaris worms are still small. Even less possible is such development from ova or larvæ in the said three organs in the case of the liver flukes, the embryos of which hatch from the ova only in water, and the larvæ of which must have passed through two different intermediate hosts, a mollusc and a fish, before they can develop within the intestine of the definitive host into the worm.

In parenthesis, certain facts regarding liver flukes are here perhaps of interest, as connecting up with statements made above with reference to the spread of bilharziosis. Cancer from liver flukes as the inciting factor was first observed at the University of Königsberg. That town is located near a bay which averages 5 miles in width. The bay is cut off from the main body of the Baltic by a peninsula 60 miles long and 1 to 2 miles wide which consists entirely of high sand dunes. For ten years there had not been a single case of cancer among the 2300 inhabitants of the peninsula, while on the opposite low, swampy mainland there were many cases of cancer during that time, though type and habits of the people in both localities are identical.³⁸ On both sides of the bay the people are heavily infested with the tapeworm *Bothriocephalus latus* (Rindfleisch, 1910, p. 14³⁴). The difference in the two localities consists in the fact of there being on the land side many fresh water streams which empty into the bay, and none such on the peninsula. As established for the nearby river Elbe,³⁹ so also these streams probably swarm with the immature larvæ of parasites requiring a mollusc for an intermediate host in order to attain the mature larval stage,³⁴ among them the larvæ of liver flukes which, after they have gone through the molluscs, which are plentiful in these streams, penetrate the scaly skin of the fish frequenting those waters and settle down

in the muscles of the same, developing no further until their particular host has been eaten by a warm-blooded being (cat, dog, man). On the peninsula, there being no streams, there are consequently no molluscs and, therefore, no larvæ of liver flukes in the fish. The inhabitants go fishing in their home waters. Those on the land side catch, and eat raw, fish infested with the larvæ of the liver flukes, those of the peninsula fish not so infested. Both catch and eat raw fish infested with the cysticercus of *Bothriocephalus latus*. Consequently tapeworm prevails on both sides of the bay, while only the inhabitants of the land side are infested with liver flukes. The latter being a cancer-inciting factor, cancer occurs on the land side, but none from that cause on the peninsula.⁴⁰

Liver flukes, when full-grown, are only 1 cm. in length by 2 mm. in width. In the small intestine they do not seem to find the suitable environment and perish therein quickly (Rindfleisch, 1910, p. 21³⁴); but thousands may be demonstrated in the liver and in the gall bladder. In such cases the latter has been found of the size of a walnut, its walls, as also those of the large ducts, being greatly thickened. Light pressure upon the gall bladder brought on the outflow from the papilla Vateri of a glassy mucus, in which masses of the worm were demonstrable (Rindfleisch, 1910, p. 4³⁴). The worms are easily overlooked and not infrequently escape detection during operation. They are translucent and of a reddish hue, so that a convolute mass of them gives the impression of a "mucoid blood coagulum." Only by careful inspection, looking against the light, do they become discernible through reflection (Askanazy, 1904³⁵). It is quite probable that invasion of the liver and of the pancreas by worms is much more frequently the cause of cancer in these organs, than is commonly supposed (Rindfleisch, 1910, p. 23³⁴).

Summary of Section on Adult Worms. Dead adult liver flukes enclosed with their ova and with cellular detritus in nodules of the biliary system or in the pancreas, also adult ascaris worms that have invaded the ducts of these organs, may, probably by the combination of mechanical pressure, foreign body irritation and toxins, produce therein a precancerous state.

*General Summary.** The three questions regarding the relation of ova, larvæ and worms to cancer incitement having been discussed, it should be mentioned again that they were selected for special consideration not so much because of the interest attaching to them *per se*, but rather as representatives of all the multifarious factors known to have set in motion, in one instance or another, a train of events which terminated in cancer. The task would, therefore, seem to remain of deducing from the foregoing and from the references features common to all the factors of which nonspecific parasites are a paradigm.

* See also the Summaries of the several sections.

1. Numerous, and among themselves unrelated factors, when impinging upon human tissue, are apt to irritate it and to set up therein a chronic morbid condition, from which a sequence of events culminating in cancer has been observed sometimes to arise. Such potentially cancerous conditions have, therefore, been termed a "precancerous state,"⁴¹ and the factors inducing them, "cancer-inciting factors."

2. Cancer-inciting factors, while capable of initiating a precancerous state, evidently do not govern the behavior of the tissue during this state, for the suspicious condition of the tissue may be aggravated, or it may become stationary, or it may recede after the initiatory irritation has ceased to exist.

3. A precancerous state appears always to be interposed between the taking-effect of the cancer-inciting factor and the state of malignancy, so that in all probability there is no *direct* relation, if any, of the two events to one another as of cause and effect.

4. The primary irritant, the cancer-inciting factor, is not a "cause of cancer." There is no knowing whether the chronic condition which it may initiate under certain circumstances in the tissue, will ever mature into definite malignancy, or will not do so.

Conclusion. During the precancerous state the fate of the patient hangs in the balance. It is, therefore, of surpassing interest that the precancerous state appears perfectly amenable to curative intervention. There is no general rule for such intervention, and the multiplicity and infinite variety of conditions surrounding the precancerous state would require the separate consideration of each individual case for the determination of the therapeutic indications (Menétrier, p. 152⁴²).

Of greater importance than to know how to treat an existing cancer would be the knowledge of how to prevent the development of a threatening cancer. Toward this end the precancerous state would seem to be the given point of attack.

Hence, location permitting, the clinical effort should always be directed toward recognizing a precancerous state, and then aborting or excising it, as the case may be.

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CARCINOMA OF THE ESOPHAGUS WITH ESPECIAL REFERENCE TO SITE.

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THE following consists of a survey of 196 cases of esophageal cancer that have accumulated during the past ten years at the Cook County Hospital, and includes a detailed study of 51 cases that have come to necropsy. Ten of the latter serve as the basis of this report. Most of the larger studies of the pathology of esophageal cancer consist of collected case reports made for statistical or other purposes. The cases herein reported are those from under one hospital roof and were followed through from the admitting and examining room to the morgue.

Among 12,000 patients who in two months sought hospitalization or advice, there were 11 cases of cancer of the esophagus in a group of 59 cases of gastrointestinal cancer. There were 37 cases of cancer of the stomach. Statistics as to the postmortem incidence of the

disease are not available. It appears, however, that they would be misleading, for the number of cases that came to necropsy seemed to be out of proportion to the number of cases of gastrointestinal cancer that were in the hospital. This was undoubtedly due to the interest in following up a case of hidden mediastinal tumor as opposed to one palpable in the abdomen.

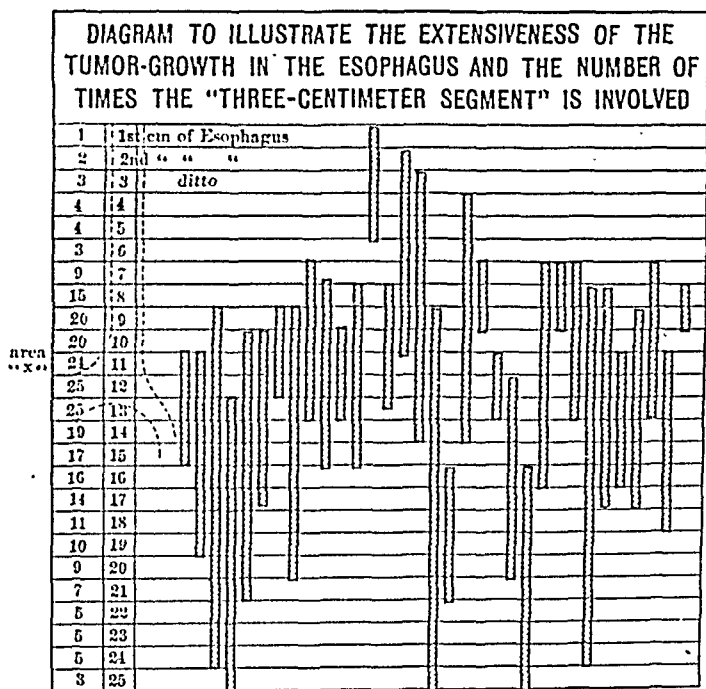
The bifurcation of the trachea has been considered by many writers to be a very common site of esophageal cancer, and perhaps this is the prevailing notion. In the pathogenesis of the disease it has been repeatedly pointed out that the tumor may originate at the site of one of the constrictions, as where the gullet is crossed by the left bronchus. We have found carcinoma of the esophagus to be a very extensive disease; and believe that the same strange interest which has allowed authors to describe the disease anatomically, with possibly the etiological idea in the background, has helped to confuse the picture of the disease. The confusion and variances that one encounters in reviewing the literature reinforces the point, as the guilt of origin is ascribed to the upper, middle, or lower parts respectively.

A brief resume of some of the larger case reports may not be amiss. Huffer mentions 857 cases, in which it is noted that the middle and lower parts are involved in 699 instances. Wessel mentions 300 collected cases of Krauchaar in which the middle part was involved in 40 per cent of the cases. Petri finds in his own group of 44 cases the lower part affected in 18, the upper part 13 times. It is interesting to note in Lerche's statistical study that in a total of 1081 cases collected from the English literature, 430 were those of upper channel involvement; whereas in a total of 1084 cases from the German literature the reverse obtains, there being only 128 instances of upper esophageal disease. The same author quotes McKenzie as having made an observation of this same fact, namely, that the upper part of the channel appears to be the more frequent site of the tumor in the English speaking people, an observation that is not entirely unamusing.

In 33 of the 51 cases we were able to tabulate the up-and-down involvement of the channel to and from definite points, such as the cricoid cartilage or cardia. It might be worth while to call attention to an error that might readily be committed. In each case the 25 or 27 cm. of esophagus could be involved, a total of 825 cm. in 33 cases. (Cunningham, average length 25 cm.) Actually a total of 276 cm. (almost exactly one-third) are involved. We find that 25 cases, that is, 75 per cent involve some part of the 3 cm. segment which we have arbitrarily placed at 11, 12, and 13 cm. of the esophagus—area "X"; this seems far out of proportion but in reality is only a few per cent—about 8 too high, a deviation which is of no value in such a small number of cases. (Kindness of Dr. Ernest B. Zeisler).

In the accompanying chart the variation in the number of cases for each centimeter of esophagus is noted. The region of the bifur-

cation (11, 12, and 13 cm.) shows the most cases—25. But we must note that the mere extension of the tumor into a region does not prove that it originates there; as far as we know, only 1 case needs to have originated in area "X," for all of the other cases involve regions outside of "X." Thus the only really valuable cases for statistical studies are those of limited extent. The evidence does point toward some connection between carcinoma of the esophagus and the region "X;" either the growth originates more frequently in "X" or having originated elsewhere, it spreads more rapidly into "X" than into other parts. If this were a report on 3300, instead of 33 cases, we should not hesitate to conclude that one or the other alternatives is correct. We feel, however, that it would be as incorrect to say that the commonest site of origin is at the bifurcation as to say, if we might employ the homely analogy, that the night hours are the commonest ones for obstetrical labor, inasmuch as labor extending over so many hours must consume some at night.



In 49 of the 51 necropsy cases there was an absence of metastases noted in 14 instances (28.5 per cent). Five of these showed a marked tendency to infiltrate the prevertebral tissues, aorta and others, and microscopic studies might have disclosed glandular metastases. There were widespread metastases to the viscera and glands of the abdomen in the 35 cases which disclosed metastatic infection. Of these the liver was involved 7 times, but always with mediastinal glandular or other visceral involvement. Petri in his group of 44 cases finds the liver to be the seat of metastatic tumor 6 times, but 4 of which involved the liver alone. Nirschl in quoting Colle's 15 cases finds the liver the seat in 6 cases, but in

only 1 was it involved alone. In the gross pathology mention should also be made of the associated vascular pathology. Tracheal or bronchial perforations exceed only a little those of aortic perforations, of which there are 4 cases. Regional thrombosis of the aorta and vena cava, respectively, were encountered in the 2 instances. In 6 other cases there was a marked fibrous union of the esophagus with the front wall of the aorta.

A pointed observation that may be made from our records is that the extensiveness of the involvement of the channel and the metastases and the duration of the symptomatology do not go hand in hand; but rather may be inversely proportional to one another. In 48 cases the average computed life history of the disease from the first complaint to the time of death is five and a half months. In 3 cases which had a clinical period of sixteen weeks, one-half of the channel was involved in an ulcerative carcinomatous process. In all but 1 there were metastases. But in those several instances where two-thirds or more of the channel was involved, it is to be noted that the duration of the disease was up to fifteen months. On the other hand, where the tumor is quite circumscribed and does not involve the channel for more than 3 cm., the duration of the symptoms was up to a year or more. There is, of course, nothing contradictory in these findings; the lack of tendency to spread explains the duration of the picture, except in those very few instances where the tumor was essentially obturating, and the patient was rapidly starved to death. We are led to conclude, however, that it is quite impossible to recognize the so-called early case, and that we know little or nothing about the extensiveness or rapid spread of the disease with the first complaints of the patient.

It is interesting to note that only 1 of the 51 cases that came to necropsy was a female; and of the group of 145 cases, only 10 were females. So low a percentage of females afflicted with the disease (5.6 per cent) we have not encountered in any series.

NOTE. Grateful acknowledgement is made of the courtesies extended by Dr. James G. Carr.

Summary. 1. Carcinoma of the esophagus is an extensive disease. In a series of 51 necropsies one-third of the esophagus was involved by the tumor growth.

2. Evidence that the disease begins at the site of the tracheal bifurcation is only presumptive. Only 1 case in this group needs to have originated there.

3. There is some relation between carcinoma of the esophagus and the region of the bifurcation. Either the growth originates there or spreads more rapidly into it.

4. It is quite impossible to recognize the so-called early case. At the time of the first complaint of the patient, there may already be extensive metastatic infection.

5. The average computed life history of the disease is five and a half months.

A FORM OF ACUTE HEMOLYTIC ANEMIA PROBABLY OF INFECTIOUS ORIGIN.

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DURING 1922 and 1923 there were admitted into this hospital three unusual cases characterized by sudden onset with elevation of temperature, leukocytosis, and a severe anemia resembling pernicious anemia, all of which symptoms promptly and rapidly disappeared following a single transfusion.

Reference to acute forms of pernicious anemia was made by Osler.¹ Elsner² mentions acute anemia of the pernicious type which may be due to syphilis, and other types in which the patients usually die within eight weeks. Krumbhaar³ also writes of cases of acute hemolytic anemias which have recovered after a single transfusion. References to clinical descriptions of such cases, however, cannot be found. It hardly seems possible that cases similar to those described in this communication have not been reported. Perhaps they are obscured under unfamiliar terminology, and for that reason have not come to the attention of the writer. That the condition is not an infrequent one is evidenced by the fact that two other cases of like nature have been seen by the writer, and his attention has been called to three more treated in other hospitals.

Diseases in which rapidly progressing anemias of unknown etiology are the cardinal symptom are exceedingly uncommon. The hemolytic anemias, acquired and congenital, are characterized by hemal impoverishment, the establishment of which requires some length of time. Acute hemorrhage alone stands out as the condition which can bring about a very rapid blood loss, that is, in a period of hours or few days. Various authors trace the occurrence of acute unexplained anemias to syphilis, and to the unknown cause of pernicious anemia. In the latter disease an acute exacerbation may take place, with a sudden increase in the degree of anemia. The acuteness, however, is a question not of days but of weeks. A variety of hemolytic agents such as arsenic, mushrooms, snake venom, and blood with a high titer of hemolysin from an incompatible donor can cause sudden and voluminous erythrocytic destruction with consequent severe and prompt anemia. This is a well-known and easily recognized group.

The cases to be described present some differences from any previously described in the available literature. They resemble one another so closely that the writer believes it justifiable to classify

them for clinical purposes in one group. The outstanding features of the cases are the acuteness of the development of the symptoms, evidences of very rapid erythrocytic destruction, extreme regenerative action of the bone marrow, rapid recovery after therapy, and the absence of sequelæ. The case reports are as follows:

Case Reports. CASE I.—B. L., male, aged nineteen years, a student of pharmacy, using tobacco in small amounts; has always been perfectly well. There is no definite history of any previous illness. Up to the time of admission his complexion was ruddy.

Present Illness. Three days before admission, he was suddenly seized with right frontal headache and pain in the right eye, which continued. He became very weak and once he fainted. The color of his skin became yellowish. On admission his pulse was 104, the temperature 102° F.

Physical Examination. The patient is well nourished, not appearing acutely ill, his skin is of an icteroid tinge, and is pale and pasty. The scleræ are definitely icteric. His teeth show repair work, his gums are normal, the tonsils and pharynx are slightly congested. The lateral lobes of the thyroid are somewhat enlarged. The lungs are normal. Examination of the heart reveals a systolic murmur at the apex, probably hemic in origin. The abdomen is not distended. The liver is felt 2 cm. below the costal margin. The spleen is palpable 8 cm. below the costal margin, is rather firm, but not tender. No other abnormalities are noted.

On admission his general condition was very poor. He presented a yellowish-green appearance, and was very weak and apathetic.

His temperature on admission was 102° F. and ranged between that figure and 101° F. for six days, after which it gradually dropped to normal and remained so. The drop in the temperature followed the transfusion.

Examination of his eyegrounds disclosed moderate-sized superficial retinal hemorrhages, localized mainly about the discs. On April 20, the fasting contents of the stomach contained no free hydrochloric acid; forty minutes after a test meal free acid was present. Extractions obtained by the Rehfuß method on April 24 and 29 contained no free acid. The feces contained no blood, ova or parasites. The Wassermann reaction was negative, his blood chemistry showed a slight hyperglycemia (150 mgm. per 100 cc blood), the blood culture was sterile. The urobilin and urobilinogen outputs were as follows:

TABLE I.

1920.		Urobilinogen, dil. units.	Urobilin, dil. units.
April 12	Urine	2,000	2,375
14	Bile	8,575	13,636
20	Feces	104,000	240,000
24	Feces	6,400	7,200

The changes in his blood picture are depicted in Chart I and described in Table II. All the evidences of a profound anemia with every manifestation of hyperfunction of the bone marrow were seen. A very close resemblance to the blood in pernicious anemia during a crisis was noted. Red cells with mitotic, pyknotic, fragmented, degenerated and freshly extruded nuclei were found. Megaloblasts were easily demonstrated. A high degree of anisocytosis, poikilocytosis, numerous polychromatic cells, and cells with basophilic granulation (stippling) dominated the picture. Many free extruded nuclei were scattered throughout the preparation. A pronounced macrocytosis and microcytosis existed, and most of the cells appeared hyperchromic.

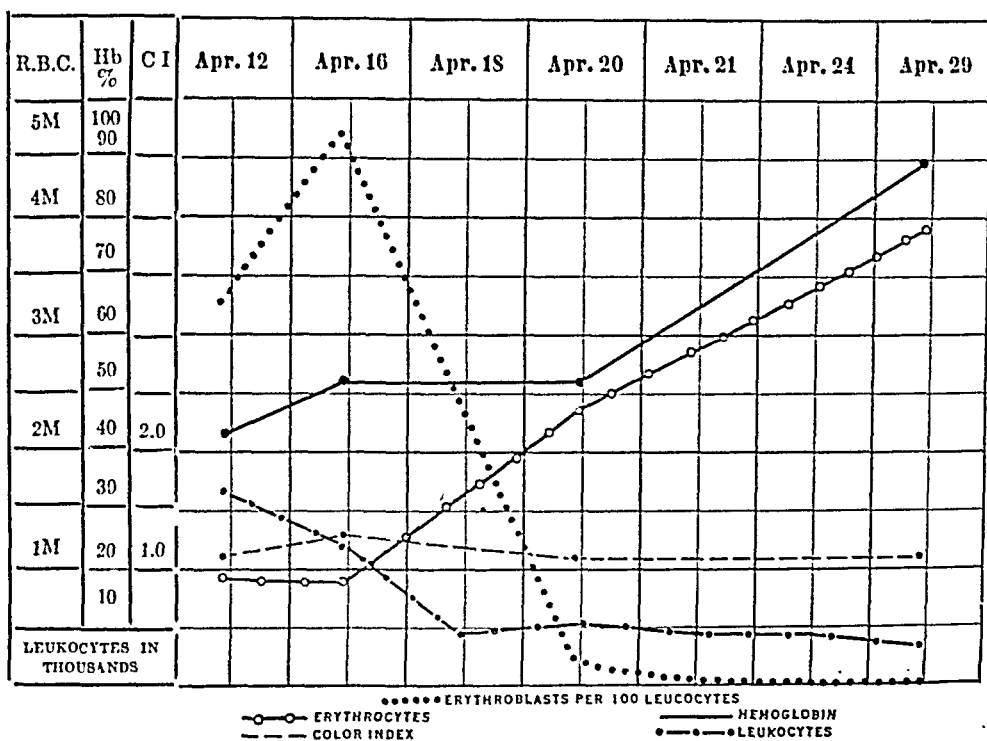


CHART I.

The great numbers of erythroblasts seen, made it apparent that the leukocyte count as estimated in the usual way was erroneous. Correction was therefore made by subtracting from the total number of cells per cubic centimeter as estimated from the white blood cell pipette, the erythroblasts as estimated in the stained preparations. Since this article was written, the author has found a description of a similar method used by N. Rosenthal in 1914.⁴ The leukocytic picture betrayed evidences of active response to stimulation. The lymphocytes were but slightly increased in proportion to the myeloid cells. The latter showed in small quantities every type of cell associated with myeloid leukemia, some undifferentiated, and others in various stages of differentiation.

TABLE II

Date, 1922.	Hemoglobin, per cent (Dare).	Erythrocytes per c.mm.	Color index.	Platelets per c.mm.	Leukoocytes per c.mm.	Polymorphonuclears.	Eosinophils.	Basophils.	Mononuclears.	Transitionals.	Lymphocytes.	Myeloblasts.	Neutrophilic myelocytes.	Basophilic myelocytes.	Metamyelocytes.	Normoblasts, per 100 leukocytes.	Megaloblasts, per 100 leukocytes.	Stained preparations.
April 11	55.5	0.5	...	8.0	2.0	24.5	7.00	2.5	...	8.0	63.5	3.5	Anisocytosis, poikilocytosis, polychromasia, stippling, hyperchromia and marked macrocytosis.
12	43	1,990,000	1.10	210,000	33,615	55.0	2.00	14.0	...	14.0	...	15.0	60.0	6.0	
16	52	1,870,000	1.40	340,000	25,802	51.0	2.25	0.25	3.5	4.5	28.5	0.75	2.75	0.75	5.7	87.0	6.0	
18	8,381	48.0	2.00	0.08	40.1	1.00	7.90	...	0.9	44.0	5.0	
20	52	2,310,000	1.10	260,000	10,000	48.0	8.0	...	43.0	1.0	0	5.0	
21	7,400	52.0	1.00	...	3.0	...	44.0	0	1.0	Less than above.
24	7,400	35.0	1.00	...	6.0	...	58.0	0	0	
29	90	3,890,000	1.11	250,000	6,100	52.0	1.00	...	18.0	...	28.0	0	0	Slight anisocytosis and hyperchromia.

The lymphocytes, however, all appeared mature. These findings pointed to the stimulating action of some irritant, resulting in hyperfunction of hemopoiesis affecting the leukopoietic and erythropoietic elements equally. He rapidly grew worse, and after five days a transfusion of 350 cc of unmodified blood was given. The change in his condition was startling. He began to improve immediately, grew stronger, became brighter and quickly regained his normal status. The immature cells, both of the red and white series disappeared completely from the circulation within the five days following the initial and only transfusion. On discharge, no immature or developmental forms were found, there remained but a slight degree of anisocytosis and poikilocytosis and an appearance of hyperchromemia. Reëxamination several months later failed to show any evidence of disease. The blood examination was normal.

CASE II.—A. F., male, aged sixteen months, was admitted May 28, 1922. He was a perfectly normal child, always well except for an occasional slight cold. A doubtful history of having swallowed camphor some days before admission was elicited. Three days before admission he had three loose-bowel movements. In the evening he was restless and cried the greater part of the night; the next day his skin became yellowish in appearance, and the color rapidly deepened.

Physical examination shows a male child, well developed and well nourished. His skin is extremely pale and has a greenish-yellow tinge. The mucous membranes are blanched—they appear almost bloodless. The tonsils are enlarged. The lungs and heart are normal. The abdomen is slightly distended, the spleen edge is just palpable in the left flank.

TABLE III.

Date.	Hemoglobin, per cent (Dare).	Erythrocytes per c.mm.	Color index.	Leukocytes per c.mm.	Polymorphonuclears.	Eosinophils.	Mononuclears.	Lymphocytes.	Erythroblasts per 100 leukocytes.	Stained preparations.
May 28, 1922	20	960,000	1.04	52,000	24	..	2	44	32	Transfusion. Anisocytosis; poikilocytosis; marked macrocytosis.
29, 1922	30	990,000	1.50	32,200	50	50	0	
30, 1922	35	1,450,000	1.20	18,400	43	6	6	45	0	
June 1, 1922	73	3,400,000	1.07	12,800	29	2	9	60	0	Normal.
July 17, 1924	65	5,720,000	..	12,200	44	3	1	52	0	

His temperature on admission was 100.8° F. but within about four hours rose to 103.6° F. The blood picture resembled that of

Case I. The anemia was much more profound, and evidences of regeneration were not as marked. Apparently the process was of much shorter duration, the insult to the reticulo endothelial system greater. His condition was so desperate (Chart II and Table III) that 120 cc. of unmodified blood were transfused on the day of admission, with the most gratifying result. Improvement was apparent at once, his temperature reaching a normal level within twenty-four hours, and three weeks after admission he was discharged well. He was brought back for reëxamination July 17, 1924, in perfect physical condition and with normal blood pressure.

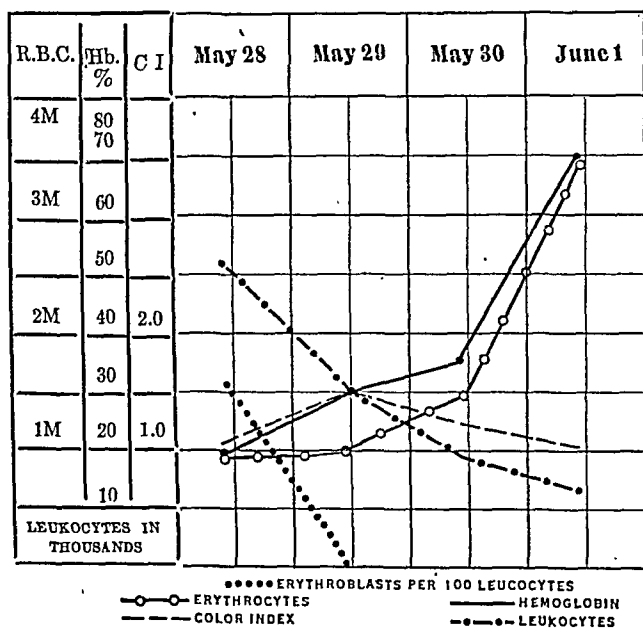


CHART II.

CASE III.—L. B., female, aged thirty-five years, married, housewife, was admitted March 9, 1923. Her chief complaints were pain in the back, extremities, and head lasting six days. She was always well up to two years ago, when she was told she had a "leaky" heart. She suffered from dyspnea and palpitation on slight exertion, and also from car sickness. She had been married ten years, and had two children. Her menstrual history was normal. About two weeks before admission she suffered from an attack of what she thought was "grippe." She remained in bed for two or three days, with a temperature ranging around 101° F. When she left bed, she noticed pains in the back of a sticking nature, and dragging pains in the extremities. These pains gradually increased in severity until six days before admission, when she was compelled to return to bed. Her temperature at this time ranged between 101° F and 102° F. The next day she vomited, and the vomiting continued up to the time of admission. For the last

two or three days she had a cough. She noticed that her skin had become yellow.

Physical Examination. The patient appears acutely ill. She is fairly well developed and nourished. Her skin is pale and has a yellowish tint; the conjunctivæ are icteric. The teeth are in fairly good condition, the tongue is markedly coated, the throat is congested, the larynx negative. The apex of the heart is in the fifth intercostal space at 1.2 cm. ($\frac{1}{2}$ inch) outside the nipple line. There is a blowing systolic murmur over the apical area which is transmitted to the axilla and upward toward the base. The liver is palpable 2 cm. below the costal margin, the spleen is not felt.

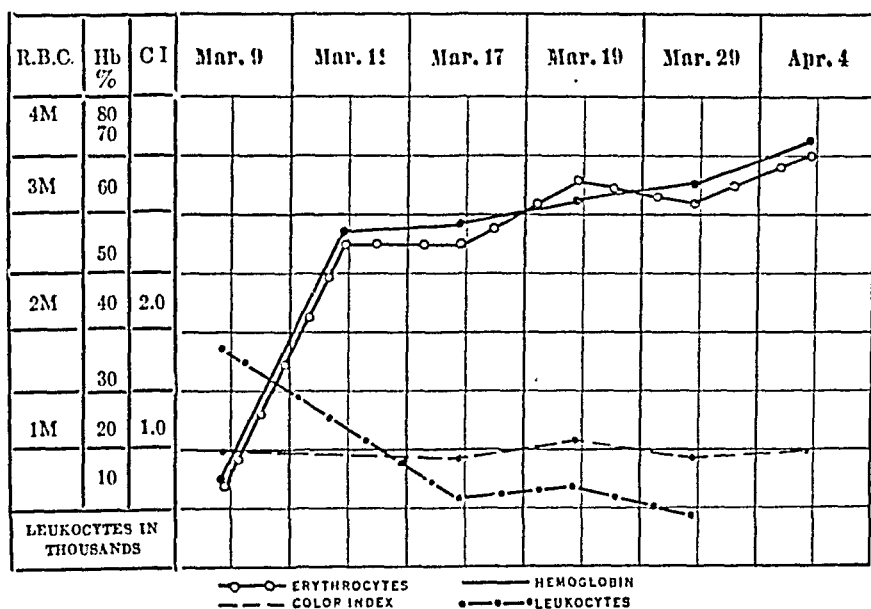


CHART III.

The temperature on admission was 102.4° F. The urine was negative except for a faint trace of albumin. The blood culture was sterile. The Wassermann reaction was negative. Examination of feces showed no ova or parasites.

The examination of the fundus showed conditions similar to those in Case I. Retinal hemorrhages were seen in both eyes, mainly in the regions of the discs.

Because of the profound anemia, immediate transfusion of 600 cc. of whole blood from a polycythemic patient (erythrocytes 12,000,000 per cc.) was done. Within twelve hours the temperature fell from 104° F. to normal, ranged about 101° F. for two days, gradually dropped to normal and remained there. The blood picture resembled that of Case I in all respects excepting in degree. The extreme erythropenia and leukocytosis were almost duplicates of Case II. The change in the blood picture after transfusion was similar (Chart III, Table IV). During convalescence she complained of

TABLE IV.

Date.	Hemo- globin, per cent (Dare).	Erythro- cytes, per cmm.	Color index.	Platelets per c.mm.	Leuko- cytes per c.mm.	Poly- morpho- nuclears.	Eosino- phils.	Baso- phils.	Mono- nuclears.	Lympho- cytes.	Myelo- cytes.	Erythro- blasts.	Stained preparations.
Mar. 9, 1923	14	780,000	0.95	150,000	37,000	81	2	10	7	Present	Anisocytosis transfu- sion.
11, 1923	55	2,800,000	0.97									0	Slight anisocytosis.
17, 1923	55	2,920,000	0.95	350,000	12,000	68	2	1	3	26	...	0	
19, 1923	65	3,100,000	1.05	...	12,900	73	3	24	...	0	
29, 1923	62	3,310,000	0.93	260,000	9,800	52	1	1	6	40	Slight anisocytosis and poikilocytosis.
April 4, 1923	70	3,640,000	0.96	
May 13, 1924	77	5,040,000	0.95	...	7,200	66	4	...	3	27	...	0	Normal.

persistent headache for which lumbar puncture was done followed by relief. Examination of the fluid showed no abnormalities. She was discharged well on April 16. She reported for reexamination on May 13, 1924. Considering the previous cardiac condition, her status was normal and her blood picture was normal.

Comments. The onset was very sudden in 2 of the cases, a history of but three days' duration being elicited. In 1, the disease was ushered in with a slight diarrhea; in the second, with a severe headache. In the third instance, the onset was more complicated. Apparently she first suffered from pain in the back and extremities, thought to be of a "grippal" nature. The symptoms in all 3 instances were rapidly followed by weakness, pallor and slight icterus, and in 2 instances by vomiting.

Physical examination showed the patients to be intensely anemic, somewhat jaundiced and febrile. The spleens of 2 were palpable, but were not tender. In 2 there was definite hepatic enlargement. There was no bone marrow tenderness present in any of the cases. In 2 of the patients the eyegrounds revealed recent changes of a type commonly seen in pernicious anemia. Blood examinations revealed evidences of a profound anemia of a hyperchromic type and of an active myeloid production. At the time of admission a marked leukocytosis prevailed in all, being 52,000, 37,000 and 25,800 per c.mm., respectively, with a neutrophilic polymorphonucleosis of 81 per cent, 55 per cent and 51 per cent. In all cases the study of the erythrocytes showed changes indicative of a profound bone-marrow disturbance. All the associated changes present in severe pernicious anemia during a blastic crisis were observed. The number of normoblasts was enormous, in one instance amounting to about 3000 per c.mm. The fragility of the red cells was tested in the adults and was found to be normal.

The youth, being the first case admitted, was studied for several days, the transfusion being performed five days later. Before the transfusion, the course of the disease was steadily downward and a fatal termination seemed almost inevitable. Because of the favorable effect of the therapeutic measure adopted in this case and the grave condition of the 2 later cases, they were transfused within a few hours after admission with similar gratifying effects. The improvement in all was evident almost immediately, recovery was rapid and permanent, as proved by reexaminations a year and two years later.

Thus, 3 cases similar in onset, symptomatology, course and response to treatment were observed. The anemia, which was the obvious outstanding, predominant, and the most alarming symptom, was due apparently to rapid blood destruction from either a bacterial or toxic agent. The evidence which points to infection as the cause, is the acute onset, temperature (not completely explain-

able by the anemia), leukocytosis, the enlarged spleen and possibly the specific effect of the transfusion. The latter did not produce benefit by replacement, since, in all the cases the enormous increase in the red cell content within the subsequent forty-eight hours cannot be so explained. The spleen, *per se*, apparently played only a secondary role in the hemolytic process, since the individuals were not anemic previous to this time and the enlargements promptly disappeared with recovery. In one instance, there was no demonstrable splenic enlargement. The cases closely resemble pernicious anemia in all ways excepting in the absence of previous history pointing to its existence, and in the complete recovery of the patients without sequelæ. The leukocytosis cannot be wholly accounted for by Minot's⁵ explanation "When the marrow is working hard to form blood and is not succeeding well, it may be reflected in the blood picture of the white cells." This may explain the occasional high leukocyte counts and the few myelocytes that are sometimes seen during the course of pernicious anemia, but not the enormous leukocytoses and the relatively large numbers of immature cells present in these cases. There is no doubt that part of the leukocytosis is due to the compensatory effort of the bone marrow to replace the destroyed red cells involving at the same time the leukopoietic factor. However, a combination of factors offers a more satisfactory reason for the white blood picture. It is quite plausible that the exciting factor, probably infectious in nature, exercises a selective action on the cells of the reticulo endothelial system (hemolyto-poietic system of Krumbhaar).⁶ Naegeli⁷ suggests that the hemolytic anemias are susceptible of that explanation. The reticulo endothelial system is made up of the productive, as well as the destructive components, of the hemopoietic structures. Therefore, a toxin acting as an irritating stimulus could well exert its influence on both components of this system with consequent increase of the blood destruction by a process of stimulation; similarly, this stimulant, affecting the bone marrow, would thus account for the appearance of the enormous numbers of immature and blastic cells of both red and white series. Furthermore, in the case of the red cell, destruction occurred more rapidly than production, resulting in a severe anemia. On the other hand, the destruction of the white cells apparently not being dependent on the reticulo endothelial system, and therefore not subject to the pathologic influence of the disease, proceeded at normal rates and resulted in a heaping up of fully developed and immature leukocytes in the circulation. In other words, the leukocytosis can be accounted for by three factors, infection, increased production, due to the stimulating action of the toxin, and heaping up. This explanation is offered as a tentative hypothesis to stimulate investigation along these lines.

The important practical point to be emphasized is the prompt

cessation of the pathological process after transfusion. To attempt to explain its action is purely speculative, but it acted as a specific in the 3 cases herein described and in 3 others to which the writer's attention has since been called.

Acknowledgment is expressed to the services of the late Dr. Leon Louria and Dr. W. K. Jacobs for permission to utilize the clinical material.

Conclusions. 1. Three cases, of a type hitherto undescribed in the available literature, characterized by sudden onset, fever, leukocytosis and severe anemia, are described.

2. Alterations in the blood, similar to those seen in pernicious anemia were found.

3. Evidences of rapid and enormous blood destruction were present.

4. The behavior suggests an infection with selective action concentrated on the reticulo endothelial system.

5. Prompt and permanent recovery followed a single transfusion of unmodified blood.

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CLINICAL VALUE OF SOME RECENT TESTS FOR LIVER FUNCTION.*

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WE have made a comparative study of some of the newer and more promising tests for liver function. Our object has been to learn something of their relative value for diagnosis and prognosis and to find out, if possible, what tests are most helpful and best suited for the routine clinical study of cases with suspected or obvious liver disease. For this purpose, we used the Rowntree-

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Rosenthal test of dye excretion, the quantitative estimation of bilirubinemia by means of the icterus index as described by Bernheim¹ and the qualitative determination of bilirubinemia by the methods of van den Bergh and Fouchet.

Rowntree-Rosenthal Test. The liver function test now apparently receiving the greatest attention in this country is that of Rowntree and Rosenthal, based on the ability of the liver to excrete the dye substance, phenoltetrachlorophthalein, from the blood stream. Five milligrams of phenoltetrachlorophthalein per kilo of body weight are given intravenously and small specimens of blood are collected after fifteen minutes and again after an hour. The amount of dye in the serum of each specimen is then determined by colorimetric comparison. Normally from 3 to 5 per cent of dye is present in the blood serum at the end of fifteen minutes, and none at the end of an hour. With liver damage there is retention of the dye in the blood. Its estimation supposedly gives quantitative figures of the extent of impaired hepatic function.

Estimation of Bilirubinemia by Icterus Index. Recent work by Mann² and his co-workers has shown that the liver is not essential for the production of the bile pigment, bilirubin, and that a high percentage of it may be formed outside of the liver. But the liver is the sole excretory organ for this pigment in health, and upon this fact functional tests have been worked out by van den Bergh³ and Meulengracht.⁴ When bilirubin is not excreted by the normal channels through the liver it accumulates in the blood. Normally the quantity of bilirubin in the blood serum is small. The color of the serum deepens as the bilirubin increases. This occurs in certain cases of diseases of the liver and gall bladder, and in hemolytic conditions such as pernicious anemia and hemolytic jaundice. Blood serum is collected and compared in a colorimeter with an arbitrary standard, a 1 to 10,000 potassium bichromate solution. The standard solution is put in a 15-mm. cell and a reading is taken when the standard and the serum match. The standard number, 15, is then divided by the scale reading. If the color of the serum is too deep, it is diluted and the quotient is multiplied by the number of dilutions. Bernheim¹ found that in cases of clinical icterus the index was over 15, and when jaundice was absent it was below 15. As the normal range is between 2 and 5, latent jaundice is represented by figures between 6 and 16.

van den Bergh's Bilirubinemia Test. The van den Bergh qualitative test for bilirubinemia uses blood serum with Ehrlich's diazo mixture. There are two possible responses, a direct and an indirect. They supposedly differentiate between obstructive and nonobstructive jaundice, the latter arising from the direct injury to the liver cells or from jaundice of extrahepatic origin. In cases of obstructive jaundice, the color of the serum changes promptly from yellow to a pink or violet and indicates a positive direct

reaction. The direct reaction is negative in cases of nonobstructive jaundice. In the indirect van den Bergh reaction the serum is first treated with alcohol and some of the supernatant fluid is added to Ehrlich's diazo mixture. If the test is positive the pale yellow color of the serum changes to pink or violet as in the direct reaction of obstructive jaundice. The indirect reaction is positive in both obstructive and nonobstructive jaundice. Therefore, a blood serum showing a negative direct reaction but a positive indirect reaction is supposed to indicate a case of nonobstructive jaundice.

Fouchet's Bilirubinemia Test. In the Fouchet qualitative test for bilirubinemia a few drops of a reagent that oxidizes bilirubin are added to an equal amount of blood serum and mixed on a white porcelain surface. If hyperbilirubinemia is present to an extent of 1 to 60,000 or more, a green color develops which is specific for bile pigment. In normal serum bile pigment exists in a dilution of 1 to 600,000.

Clinical Results. In our series 173 patients were studied. Some had only part of the tests, but about half had all 4 tests done simultaneously one or more times. This group affords a basis of comparison of the relative clinical value of the various tests, though we will also report our results with the group in which only part of the tests were made.

Normal Control Cases without Liver Disease. There were 39 cases without suspected or proved liver damage. The icterus index was normal, (below 6) in all except 2, one a case of obesity, the other a case of pregnancy with moderately severe anemia. Rowntree-Rosenthal's dye test, done 16 times, was always normal. van den Bergh's bilirubinemia test, done 18 times, was negative in all except 2 in which the indirect reaction was weakly positive. Fouchet's bilirubinemia test in the same 18 cases was slightly positive in 3.

Cirrhosis of the Liver. Six cases of cirrhosis were studied, including 1 of syphilis of the liver and 1 of splenic anemia. The icterus index was increased in all except the case of splenic anemia, ranging from 9.3 to 23. Jaundice was uniformly present when the figures were 15 or over. Rowntree-Rosenthal's test showed a retention of the dye in the blood at the end of an hour in all except the case of splenic anemia, ranging from 7 to 15 per cent. Both the van den Bergh and Fouchet bilirubinemia tests were positive in varying degrees in all cases. One patient with cirrhosis, (Case I, Table I) a man aged twenty-nine years, had a rapid course and died four months after the onset. The retention of the dye in the blood varied little, being 12, 10 and 16 per cent, while the icterus index rose steadily from the first determination 10, to 45 shortly before death. Here the icterus index seemed to give a clue about the prognosis while the dye test did not. As the case of syphilis of the liver, (Case III, Table I) improved under treatment, the icterus-

index and the dye-retention figures both fell, and about equally. Before splenectomy, the case of splenic anemia, (Case VI, Table I) showed normal icterus-index and dye-retention figures. These results seemed to indicate good liver function and a favorable case for operation. At operation the liver appeared normal to inspection although slightly enlarged. Following operation the patient made a good recovery and has remained well nine months.

TABLE I.—LIVER CIRRHOSIS.

No.	Icterus index.	Percentage of dye in blood after		van den Bergh.		Fouchet.	Icterus.	Liver enlargement.	Remarks.
		15 min.	60 min.	Direct.	In-direct.				
I . .	10.7	12.0	10.0	+	++	++	0	+	Typical cirrhosis; died in 4 months.
	25.0			++	++	++	+	+	
	30.0	14.0	16.0	++	+++	++	+	+	
	30.0			++	+++	++	+	+	
II . .	45.0	10.0	12.5	++	+++	++	+	+	Typical cirrhosis; duration, 10 months.
	9.3	10.0	7.0	+	+++	+++	0	++	
III . .	12.5	7.5	9.0	0	+	+	0	++	Clinical picture of 'cirrhosis; Wassermann, + + + +; ascites, + +; improved with arsphenamin.
	17.4	10.0	12.5	0	+	+	+	++	
	15.0			++	++	+	+	++	
	11.0	5.0	7.0	+	++	+	0	++	
IV . .	23.0	14.0	10.0	0	+++	+	++	++	Typical cirrhosis; repeated paracentesis; spleen enlarged.
	15.0	0	++	+	+	++	
V . .	15.0						0	+	Typical cirrhosis.
VI . .	6.0	5.0	0	0	+	+	0	++	Splenic anemia; no ascites; liver 5 cm. below costal margin.

Metastases in the Liver. Twenty-one cases of malignancy were studied in which there was a possibility of liver metastases. In 10, operation confirmed the diagnosis and demonstrated the presence or absence of extensive metastases. All cases (5) showing extensive metastases at operation had an increased icterus index, ranging from 8.2 to 157, and dye retention in the serum at the end of an hour, varying from 15 to 22 per cent. Here the dye test seemed the better indicator of the extent of liver metastases. The van den Bergh and Fouchet bilirubinemia tests were slightly positive when the icterus index was over 6 and strongly positive when it was over 10. In a general way the nonoperated cases gave similar results, though of course, the question of liver metastases could not be fully settled. The tests gave no help in detecting cases with slight liver involvement.

Catarrhal Jaundice and Acute Yellow Atrophy. These two conditions are grouped together because of the seemingly close relationship between them and because the tests promise help in their differentiation. The case of acute yellow atrophy, (Case VI, Table III) had an icterus index of 130 with strongly positive van den Bergh and Fouchet reactions. Unfortunately, a dye test was

TABLE II.—METASTASES IN THE LIVER. (OPERATED CASES.)

No.	Icterus index.	Percentage of dye in blood after		van den Bergh.		Fouchet.	Icterus.	Liver enlargement.	Remarks.
		15 min.	60 min.	Direct.	Indirect.				
I . .	8.2	13	15	++	++	++	0	+	Carcinoma of stomach; liver metastases, ++.
II . .	100.8	14	22	++++	++++	++++	++++	+++	Carcinoma of head of pancreas; liver metastases, +++++.
III . .	24.0	14	18½	++++	++++	++++	+	++	Carcinoma of pancreas; metastases, +++++.
IV . .	157.0	15	20	++++	++++	++++	++++	+	Carcinoma of head of pancreas; metastases, +++++.
V . .	72.0	18	22	++++	++++	++++	+++	++	Carcinoma of stomach; metastases, +++++.
VI . .	4.2	6	Tr.	0	0	0	0	+	Carcinoma of cervix of uterus; metastasis, none.
VII . .	3.8	5	0	0	0	0	0	0	Carcinoma of stomach; metastases, +
VIII . .	6.0	3	0	0	+	0	0	0	Carcinoma of stomach; malignant ulcer; metastases, none.
IX . .	3.6	4	0	0	0	+	0	0	Carcinoma of prostate; metastases, none.
X . .	6.0	5	0	0	+	+	0	0	Hypernephroma; metastases, none.

TABLE III.—CATARRHAL JAUNDICE—ACUTE YELLOW ATROPHY.

No.	Icterus index.	Percentage of dye in blood after		van den Bergh.		Fouchet.	Icterus.	Liver enlargement.	Remarks.
		15 min.	60 min.	Direct.	Indirect.				
I . .	115 (4 days later)	++++	++++	++++	++++	0	Catarrhal jaundice.
II . .	30 (8 days later)	20	20	++++	++++	++++	++	0	Catarrhal jaundice; first tested after 5 weeks of jaundice.
	62 (12 days later)	14	20	++++	++++	++++	+++	0	
III . .	30.2 (5 days after operation)	12	15	++++	++++	++++	++	0	Catarrhal jaundice (malignancy suspected); operation with negative findings; first tested after 4 weeks of jaundice.
	225 (12 days after operation)	15	20	++++	++++	++++	++++	+	
	220 (22 days after operation)	20	18	++++	++++	++++	++++	+	
	80 (12 days after operation)	18	16	++	++	++	++++	+	
IV . .	52 (22 days after operation)	12	15	++	++	++	++	+(?)	Catarrhal jaundice.
	34 (8 days later)	5	0	0	+	+	+	0	
	36 (8 days later)	12	15	+++	+++	+++	++	0	
V . .	16 (8 days later)	12	12	0	+++	++	+	0	Catarrhal jaundice.
	151	+++	+++	+++	++++	++	
	93	++	++	++	++++	++	
VI . .	28	0	++	+	++	+	Acute yellow atrophy; necropsy.
	130	++++	++++	++++	++++	0	

not made. Seven cases of catarrhal jaundice had icterus index figures ranging from 225, (the highest obtained) during the height of the disease, to 16 during the stage of decline. Serum dye retention varied from 20 per cent to none at the end of an hour, according to the stage of the disease. Results with the van den Bergh and Fouchet tests declined from very strongly positive reactions to negative as the condition cleared up, the indirect van den Bergh positive reaction being the last to disappear. Dye retention declined more slowly during convalescence than the icterus index, and would seem, therefore, to be of less value than the latter in differentiating severe catarrhal jaundice from malignancy or acute yellow atrophy. One case of catarrhal jaundice of five weeks' duration (Case II, Table III), for example, was thought at first to be a possible malignancy. The dye retention in the serum remained about the same, but a rapid fall in the icterus index before the intensity of the jaundice diminished or the stools showed bile, was the first indication that we were dealing with a benign form of jaundice. Another case of catarrhal jaundice of four weeks' duration (Case III, Table III) was operated upon for possible malignancy with negative findings. A few days later the icterus index fell rapidly and the patient went on to an uneventful recovery. Had there been a delay until the icterus index had dropped, the operation might have been avoided.

TABLE IV.—CARDIAC DECOMPENSATION (8 CASES).

No.	Icterus index.	Percentage of dye in blood after		van den Bergh.		Fouchet.	Icterus.	Liver enlargement.	Remarks.
		15 min.	60 min.	Direct.	Indirect.				
I . .	129.0	8	12	+++	+++	+++	+++	+++	Mitral; fibrillation; died in 1 month.
II . .	10.0	10	9	0	+	0	0	+++	Mitral; anasarca; marked improvement.
III . .	10.2	5	0	0	+	0	0	+++	Syphilitic aortitis; marked improvement.
IV . .	18.7	5	0	0	+	0	+	+++	Mitral and tricuspid; died in 7 weeks.
V . .	10.0	++	+	+	0	+++	Valvular disease; anasarca; died in 10 days.
VI . .	22.0 30.0	5 ..	7 ..	+++	+++	++	+	+++	Valvular disease; fibrillation; died in 2 months.
VII . .	5.0	5	0	0	0	0	0	+	Arteriosclerosis; coronary disease; died.
VIII . .	8.8	6	0	+	+	+	0	+++	Valvular disease; fibrillation; moderate improvement.

Passive Congestion of the Liver from Cardiac Decompensation. Mild degrees of a jaundice and liver enlargement are rather common in cardiac decompensation. In 15 such cases, the icterus index seemed to follow rather closely the degree of cardiac decompensation. Cases with little or no decompensation all had figures below 8.

All cases with index figures above 16—4 in this series—died within two months. Two cases with slightly enlarged livers but no icterus returned normal figures though the prognosis was apparently quite poor. Our findings in general, therefore, agreed with those of Bernheim¹ who found that the icterus index was of value in determining the prognosis and the degree of decompensation.

Dye retention did not seem to follow very closely increases in the icterus index. We were unable to establish any definite relationship between either degree of decompensation or prognosis and dye retention. van den Bergh and Fouchet bilirubinemia determinations were usually positive in varying degrees as the icterus index increased above normal. A study of our results with the four liver function tests made us feel that the icterus index alone promises some help in determining the degree of decompensation and prognosis in advanced cases of cardiac decompensation.

TABLE V.—CHOLECYSTITIS; CHOLELITHIASIS.

No.	Icterus index.	Percentage of dye in blood after		van den Bergh.		Fouchet.	Icterus.	Liver enlargement.	Remarks.
		15 min.	60 min.	Direct.	Indirect.				
I	10.5	5	0	0	+	0	0	0	Cholecystitis (operation).
II	8.7	6	0	0	++	+	0	0	Cholecystitis (operation).
III	(During attack)								
	16.2	5	0	+++	+++	+	+	0	Cholecystitis; cholelithiasis (?).
IV	(3 days later)								
	6.7	0	+	+	0	0	
IV	14.0	0	++	0	0	0	Cholecystitis, following attack.
V	144.0	15	20	++++	++++	++++	++++	+	Cholelithiasis (operation)
	187.0	++++	++++	++++	++++	+	adhesions about ducts.
VI	(6 days after operation; 1 day before death)								
VI	6.8	5	0	0	+	0	0	0	Gangrenous gall bladder, with stones (operation).
VII	(10 days after operation)								
	12.5	5	0	0	+	+	0	0	Cholelithiasis (operation).
VIII	4.6	0	0	0	0	
	12.6	6	0	0	++	+	0	0	Cholecystitis (operation).
	(18 days after operation)								
	6.0	0	0	+	0	0	

Cholecystitis and Cholelithiasis. Thirty-seven cases of biliary tract disease were studied. The diagnosis was verified by operation in 24. All cases with jaundice showed icterus-index figures over 15. All the rest operated upon, (19) returned figures in the zone of latent jaundice (6 to 16) except 1. As reported by Bernheim¹ we feel that the icterus index has its greatest value in this group of cases. The only confusion that may arise, apparently, is that duodenal ulcer usually gives figures in the zone of latent jaundice; 9 out of 10 cases of duodenal ulcer in our series did this. But other methods such as roentgenographic study usually meet this difficulty. After operation and recovery the icterus index always returned to normal. With the dye test we had hoped to obtain some evidence

of impaired liver function in the hepatitis that is supposed to accompany biliary tract disease. In this we were disappointed as all cases without jaundice returned normal dye figures. Four cases with common-duct obstruction showed dye retention after one hour varying from 8 to 20 per cent. This test we believe is valuable in determining the ability of the liver to withstand the shock of operation. The van den Bergh test in this group served only to verify that the increased figures of the icterus index were due to hyperbilirubinemia. Fouchet's test for bilirubinemia we found, as Garvin⁵ recently reported, to be quite unreliable, frequently being negative in proved biliary tract disease.

Arsenical Hepatitis. Schamberg and Brown⁶ suggested "that the serum-bilirubin determination be made from time to time in patients receiving arsenical therapy as a guide to the toleration of the drug by the liver." They pointed out that it might be wise to interrupt arsenical treatment in syphilis when the serum bilirubin became higher than normal. The only case of arsenical hepatitis in our series was a woman who developed jaundice after receiving 18 injections of an arsenical. The icterus index figure during the jaundice stage was 30, but remained high, (11.2) four months after the jaundice had disappeared. Here it seemed unwise to resume the treatment until the index became normal. It is interesting to note that the serum dye test was normal both times it was done in this case.

Discussion. A careful study of our results with the icterus index and the dye retention test failed to show any uniform close agreement between them. With few exceptions cases of apparently marked impairment of liver function gave positive results with both tests. In 2 cases of cirrhosis and in some of the cases of metastatic liver carcinoma, the dye test seemed better than the icterus index in giving evidence of the degree of liver involvement. However, in every instance in our series in which there was a positive result with the dye test, the icterus index was also increased above normal. Some of the cases with low-grade jaundice, and most of the cases with latent jaundice, gave normal results with the dye test in striking contrast to the increased figures with the icterus index. There were no false positive results with the dye test. In 10 cases out of 173 we obtained increased figures for the icterus index without any adequate explanation. It is interesting to note that all cases of pernicious anemia examined (6) had an increased icterus index and normal dye test, while all cases of secondary anemia (14) had a low icterus index, thus confirming similar previous observations.

Our results have given us the impression that the icterus index is the most useful single liver function test that we have. The dye test seems to be of supplementary value in estimating liver function. The van den Bergh qualitative test distinguishes between obstructive and nonobstructive jaundice and helps to detect any false positive results with the icterus index, as it is a specific qualita-

tive test for bilirubin. The advantages which the icterus index has over most of the other functional liver tests, and especially over the dye test, are that it is simpler, easier to perform and less objectionable to the patient. Maurer and Gatewood⁷ have recently reported 3 deaths in patients two to seven days after the Rowntree-Rosenthal dye test was made. If it should be shown by other observers that such deaths are due to the administration of the dye it would impose a very serious limitation on its use in clinical medicine. However, the dye has been used by a large number of other workers, and as far as we can learn none of them report any serious development. In our series of 82 dye injections, induration of the vein at the site of injection occurred seven times and a chill twice. No toxic effects were observed.*

Conclusions. 1. The Fouchet test proved unreliable in our hands for detecting minor grades of bilirubinemia. In other respects the van den Bergh test served very well in its place.

2. The van den Bergh test has distinct value in studying liver function and jaundice. Positive results with both reactions indicate impaired liver function, but the extent must be determined by the icterus index or dye test. It helps as a specific qualitative test for bile pigment to control readings of the icterus index in the zone of latent jaundice. It distinguishes between hemolytic and obstructive jaundice.

3. Our study would seem to indicate that the icterus index is the most useful single functional liver test that we have for clinical work.

- (a) It is easily and quickly performed, unobjectionable to the patient and free from danger.
- (b) Its greatest value is in the diagnosis of cases of cholecystitis and cholelithiasis without clinical jaundice.
- (c) It is a distinct aid in distinguishing between obstructive jaundice due to malignancy and catarrhal jaundice by showing whether the jaundice is increasing, diminishing or stationary.
- (d) It is helpful in the diagnosis of cirrhosis and malignant metastases in the liver, though apparently less so than the dye retention test.
- (e) It may indicate the degree of cardiac decompensation.
- (f) It serves as a guide to the toleration of the liver to arsenicals in the treatment of syphilis.
- (g) It will determine whether obstructive jaundice has been relieved by operation.
- (h) It helps to differentiate the primary from the secondary anemias.

* Quite recently Rosenthal⁸ reported a new dye substance, bromsulphalein. This, he states, is safe and nonirritating, and expresses directly the degree of impaired liver function by the percentage present in the blood serum thirty minutes after injection. As yet it has had no general clinical application.

4. The Rowntree-Rosenthal dye test is of supplementary value in measuring liver function. For clinical work it is more complicated, more objectionable to the patient and may not be entirely free from danger.

- (a) It seems to be of greater value than the icterus index in the diagnosis of cirrhosis and malignant metastases in the liver.
- (b) In surgical cases with jaundice, the dye test helps to determine the degree of damage to the liver parenchyma and hence the surgical risk, and acts as a guide to the operative procedure to be undertaken.
- (c) Its greatest value apparently is in the diagnosis of liver disease in patients without jaundice. Here a positive result points to liver involvement, a negative result helps to rule it out.

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FURTHER CLINICAL AND OPERATIVE STUDIES OF THE ICTERUS INDEX.

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LIVER function study at present is a virile clinical subject. During the past few years there has been real progress in the development of laboratory tests of liver activity. Each of the three best known liver functions has been called into service to answer for

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the actions of the other two. Clinical experience has shown that while these three functions are probably very closely related, they may act entirely independently of each other. For example, the glycogenic function may not be influenced by the liver's inability to detoxicate proteins; and likewise, the bile-forming power of the liver may not be dependent on either of the other two. These three functions undoubtedly modify the activity of every other essential organ in the body. Therefore, every functional liver test must be interpreted in the light of the liver's influence on other organs and also the influence of other organs on the liver. There are probably still other functions. For example, the liver may exert a powerful influence on the blood-forming organs whose action in turn may certainly affect the liver.

Realizing our inability to test every function, we are convinced that certain comparatively simple tests give us much clinical help in those diseases in which liver pathology is concerned. We have endeavored to study the liver's inability to detoxicate proteins by Widal's hemoclastic crisis method. We have derived much clinical help from a study of the liver's ability to form bile and to eliminate bilirubin from the blood stream. In this study we have utilized the quantitative colorimetric method developed in the laboratory of the Lenox Hill Hospital, New York, by their chemist, Dr. Adolph Bernhard, and by Dr. H. Peter Maue,¹ following the suggestion made by Dr. De Witte Stetten.² The above group of workers gave us the very usable term "icterus index" which was later adopted by Bernheim,³ ourselves,⁴ and others. We have used the technic as given in the footnote* below and find it simple and producing very slight variation in the hands of different technicians.

This additional report is given to emphasize the benefits derived from this test in everyday practice of medicine and surgery. The quantitative serum bilirubin test or icterus index as recently reported by O'Leary⁵ from the Mayo Clinic, practically parallels the much more complicated phenoltetrachlorophthalein test of Rosenthal. The later technic requires the withdrawing of 10 cc. of blood at four different intervals, the intravenous injection of a possibly harmful dye, and a specially constructed colorimeter unsuitable to any other use. We feel that valuable as the dye tests

* Three or 4 cc. of blood are withdrawn from a vein. The blood, kept away from the light, is allowed to clot and is then centrifugalized. The supernatant serum is removed with a pipette and compared in a calorimeter with an arbitrary standard—a 1 to 10,000 potassium dichromate solution (0.05 gm. to 500 cc. of distilled water). This solution is paler than normal serum. The Bock-Benedict colorimeter which requires less serum than the Duboseq type is the one that was used in these tests. The standard solution is put into the 15-mm. cell. The reading is taken at the point on the scale at which the serum and standard match. The standard number, 15, is then divided by the scale reading. The quotient is the icterus index. For example: If the scale reading is 3 the index is 5. If the color of the serum is too deep it is necessary to dilute it with a 0.9 sodium chlorid solution. The quotient is then multiplied by the number of dilutions. For example: If the number of dilutions is 10 the index in the foregoing instance would be 50.

may be, they are still too impractical for the great mass of clinicians who need to utilize liver-function tests. Judging from the untoward results already reported, the general use of the dye tests will soon result in their general disuse. Bloom⁶ and Rosenau conclude that the use of phenoltetrachlorphthalein dye will produce a positive van den Bergh in a normal person within sixty minutes. Following their tests, 14.8 per cent of their patients developed thrombosis at the site of injection; 22.2 per cent, local reactions; and 7.4 per cent, chills. A total of 37 per cent showed untoward reactions. After careful use of phenoltetrachlorphthalein for the detection of impairment of liver-cell function, Maurer, Siegfried and L. C. Gatewood⁷ were convinced that the injection of substances of this group is not without danger. We do not wish to condemn the dye tests *in toto* or even at all if in the hands of workers who can report such results as Graham⁸ and Sherwood Moore.⁸ However, before using such tests profusely, it is well to be familiar with the works of the above quoted authors, to which group, I desire to add the recent work of Ottenberg and Abramson⁹ showing the certain and extensive liver lesions when overdoses of the dye are used experimentally.

In the effort to correlate the known functions of the liver with the clinical observations, we have of necessity noted a close concurrent relation to the behavior of the blood-stream leukocytes. We have shown previously⁴ that a bilirubinemia in typhoid fever is as constant as a leukopenia. Further, Livingston and Squires¹⁰ have shown from the Bellevue Hospital records that even typhoid perforation results in a leukocytosis in only 15 per cent of their cases, and in most of these cases, there was some other pyogenic complication. When perforation occurred at any time during the first three weeks, there was no leukocytosis at all. It is our belief that during this period the liver is then carrying its greatest strain and that its cells, unsensitized to the typhoid toxin, are in a state of protein shock. The proteopexic function of the liver is most disturbed and probably the sensitization of the cells has not yet taken place completely. At this period the shock is more in the nature of a nonspecific protein reaction. In this way, we can see a relationship between the clinical state on the one hand and these liver function tests on the other. We believe that a study of the proteopexic function in relation to the bile or bilirubin function of the liver will correlate such tests as quantitative bilirubinemia and dye elimination¹¹ with the hemoclastic shock.

When these two tests, carefully made, do not agree, then different functions of the liver are disturbed clinically. They have a right to differ at times, for their factors, though related, are variables. Realizing that the two tests show two different though related functions of the liver, we can see a closer relation of greater clinical value in the tables of Piersol and Bockus.¹¹ They interpret their charts in favor of the dye tests and to the disadvantage of the hemoclastic

TABLE I.—OPERATIVE CASES.

No.	Patient.	Icterus index.		Proven diagnosis.	Remarks.
		Before.	After.		
5	Mr. S.	8.5	4.0	Acute cholecystitis with chronic cholelithiasis	Acute infection of old condition; hepatitis modified.
7	Mrs. Y.	15.0	6.0	Vincent's angina, severe	Was icteric then; died 4 months later from cerebral hemorrhages; hepatitis.
8	Mr. O.	8.0	4.0	Chronic appendicitis with colitis and adhesions	There had been some nausea and bowel hemorrhages; light hepatitis.
9	Mrs. H.	7.4	5.0	Chronic cholecystitis and adhesions	Moderately toxic hepatitis.
10	Mrs. W.	11.5	4.0	Chronic cholecystitis and cholelithiasis	Definite hepatitis.
11	Mr. M. E.	15.4	6.0	Chronic duodenal ulcer with adhesions around gall bladder	Severe hepatitis, toxic.
13	Mrs. H.	13.5	5.1	Chronic appendicitis and colitis with gall bladder and colon adhesions; blocking	Toxic hepatitis.
14	Mrs. F.	8.8	5.0	Chronic colitis with adhesions	There was nausea and hepatitis.
15	Mrs. H.	6.8	5.0	Duodenal and hepatic flexure with adhesions	There were severe toxic nervous spells.
16	Miss F.	9.5	4.0	Chronic gall bladder and appendix	Severe toxic spells.
17	Mrs. B.	7.2	4.0	Chronic appendicitis with colitis	No evidence of hepatitis.
18	Mrs. C.	8.2	5.0	Chronic appendicitis with duodenal adhesions and chronic gall bladder	The toxemia was moderate.
19	Mrs. L.	15.1	7.0	Colon adhesions up to mid-transverse colon	Dizziness during attacks severe; after operation, completely relieved.
22	Mrs. H.	12.2	6.0	Chronic appendicitis and cecal and hepatic flexure; adhesions of gall bladder	Very much evidence of hepatitis.
23	E. W.	20.0	7.0	Chronic cholecystitis and hepatitis	<i>Had acute exacerbations.</i>
24	Mr. M.	18.0	7.2	Chronic appendicitis and cholecystitis	Before operation, 11.5; after anesthetic, 13.5; postoperative, 13.5; 4 days later, 17.4; 21 days later, 8.8; 12 hours after transfusion index was 39.5 and heart nearly failed.
26	Mrs. L.	26.6	7.0	Chronic cholecystitis	Severe hepatitis.
27	Mr. S.	12.5	7.0	Chronic appendicitis and pernicious anemia and duodenal adhesions	
33	Mrs. S.	8.8	5.0	Chronic gall bladder and stones with adhesions	
38	Mrs. P.	8.7	6.0	Chronic appendicitis with adhesions; dermoid of uterus; psoriasis	
43	Mrs. M. A.	15.0	6.4	Chronic cholecystitis and stones	Early attacks, 15; 1 day postoperative, 13; 5 days postoperative, 8.3; 16 days postoperative, 6.4.
37	R. G.	12.0	6.0	Duodenal adhesions	Mental depression; hepatitis.

crisis because they emphasize the dye or bilirubin eliminative function as of greater value than the protein detoxication function. These functions are undoubtedly correlated and probably inseparable. The above authors¹¹ found the dye retention was very high when the icterus was very intense, but the degree of dye retention did not parallel the intensity of the jaundice. When the dye retention was great, urobilin was present in the urine, but it was absent when the dysfunction was slight. These observations would seem to favor the quantitative bilirubinemia determination or icterus index, as the test of choice among those in use at the present time. New dyes are being tested by Rosenthal and White.¹² A simpler technic and a less toxic dye may bring this test into greater clinical usefulness than any previously reported.

On the previous page we have given our tabulation and study of a considerable group of cases not previously recorded. The first group consists of 22 cases on which a liver dysfunction was definitely diagnosed preoperatively. There was an operative necessity in each case. The average preoperative icterus index was 12.3 and the postoperative index was 5.5. Operation confirmed every diagnosis.

The operative cases in which the index was 6 or below were grouped. The average preoperative index was 5.7 and the postoperative index was 5.3. In no case was there any suggestion of a hepatitis. The absence of liver or gall bladder disease could be checked from any of our three sources of diagnosis, namely, icterus index, clinical observations, or operative findings.

TABLE II.—OPERATED CASES, ICTERUS INDEX 6 AND BELOW—NO HEPATIC DISEASE SUSPECTED.

No.	Patient.	Index.		Proven diagnosis.	Remarks.
		Before.	After.		
1	Mrs. C.	6.0	6.0	Chronic appendicitis and colitis with adhesions	No hepatitis; arthritis.
2	Mrs. T.	6.0	6.0	Chronic appendicitis and chronic nephrolithiasis	Toxic, but no hepatitis.
3	Miss D.	7.0	6.0	Twisted ped., 1st; acute intestinal obs., 2d	No reason to suspect liver damage.
4	B. M. S.	6.0	6.0	Gastric adhesions about old gastroenterostomy	No blocking of bile ducts.
6	Mrs. Y.	4.3	4.3	Chronic appendicitis and colitis	No hepatitis.
12	Mrs. M.	5.0	5.0	Chronic appendicitis	More pain than toxemia.
31	Mrs. Z.	5.4	5.0	Chronic appendicitis with adhesions, not obstructing	No hepatitis.
32	Mrs. H.	5.8	5.0	Chronic appendicitis with adhesions	Eyes disturbed.
121	Miss H.	6.0	5.0	Colon adhesions	No hepatitis.

A group of 18 cases could be classed as toxic by the symptoms of migraine, biliousness, severe dizziness, and toxic convulsions. All these cases carried intestinal protozoa. Their average counts were: Leukocytes, 6500; neutrophils, 57 per cent; mononuclears, 43 per cent; icterus index average was 13.4. Improvement of the condition invariably was accompanied by a lowered index.

TABLE III.—TOXIC CASES.

Case.	White blood cells.	Icterus index.	Neutrophils.	Mono-nuclears.
P.	7200	12.5	43	57
M.	6400	9.0	51	49
M. C.	7800	15.0	56	41
B.	7000	15.0	55	45
M.	8800	19.0	71	29
P.	6200	8.0	58	42
D. B.	5800	15.0	58	42
Mrs. L.	5800	10.0	65	35
B.	7100	15.0	71	29
N. R. W.	3600	16.0	61	39
H.	6000	18.5	67	33
H.	6600	12.2	60	40
M.	6100	20.0	56	44
Ma.	6000	5.0	56	44
H.	5200	5.8	57	43
C.	6600	20.0	56	44
Co	7500	12.5	56	44
H.	7800	18.0	43	57

Table IV represents a small group where a toxic hepatitis was undoubtedly present clinically. There were 6 cases with an average index of 14.9. Operation proved the diagnosis in every case.

TABLE IV.—HIGH INDEX WITH HEPATITIS ALONE—AND TOXEMIA.

No.	Patient.	Index.		Reasons.
		Before.	After.	
7	Mrs. Y.	15.0	7.2	Vincent's angina,
11	Mr. M. K.	15.4	5.6	Duodenal ulcer with adhesions.
13	Mrs. H.	13.5	5.1	Adhesions about duodenum and chronic appendicitis.
19	Mrs. L.	15.0	7.0	Adhesions cecal and flexural.
24	Mr. M.	18.0	7.0	Appendicitis and gall bladder.
37	R. G.	12.0	6.0	Appendicitis and duodenal adhesions, mental.

The index in the appendicitis and mild colitis cases averaged 6.5 as proven by operative procedure.

There were 9 cases in which the gall bladder was definitely infected in such a way as to give either a blocking or an ascending hepatitis. The average preoperative index was 13.5 and the post-operative taken from two to three weeks later was 5.5.

TABLE V.—INDEX, WITH GALL-BLADDER DEFINITELY INFECTED—
CHRONIC.

No.	Patient.	Index.		Diagnosis.
		Before.	After.	
5	Mr. S.	8.5	4.0	Acute cholecystitis.
10	Mrs. W.	11.5	4.2	Chronic and acute cholecystitis.
16	Miss F.	9.5	6.0	Chronic cholecystitis and appendicitis.
23	W.	20.0	7.0	Chronic and acute cholecystitis.
24	M.	15.0	7.0	Appendicitis and cholecystitis.
26	L.	26.6	7.0	Chronic cholecystitis.
33	Mrs. S.	8.0	5.2	Chronic cholecystitis and colitis.
43	Mrs. M. A.	15.0	5.0	Chronic cholecystitis with stones.
9	Mrs. H.	7.5	5.0	Chronic cholecystitis.

There were 42 nonoperative cases in which the symptoms, physical findings, history and roentgen ray would definitely diagnose liver and gall bladder disease. The average icterus index was 13.8 in this group.

TABLE VI.—NONOPERATIVE CASES IN WHICH SYMPTOMS AND ROENT-
GEN-RAY POINT CLEARLY TO GALL-BLADDER AND HEPATITIS.

No.	Patient.	Index.	Diagnosis.
28	Mr. J.	9.6	Cholecystitis and hepatitis.
39	Mrs. C.	20.0	Hepatitis, cardiac.
41	Mr. L.	18.0	Amebic hepatitis.
42	Mrs. C.	12.5	Amebic hepatitis.
46	Miss H.	8.6	Colitis and gall bladder, hepatitis.
49	P. P.	18.0	Cholecystitis.
55	Mr. L.	12.0	Cholecystitis.
58	Mr. W.	11.2	Hepatitis.
61	Mr. Wi.	11.2	Hepatitis and appendicitis.
62	Mrs. P.	12.5	Hepatitis, colitis and arthritis.
63	Mr. M.	9.5	Hepatitis and gall bladder.
67	Mrs. M. C.	15.0	Hepatitis and lues.
68	Mrs. B.	15.0	Hepatitis and gall bladder.
69	J. M.	19.0	Hepatitis and polycythemia.
70	Miss R.	18.0	Cholecystitis.
71	Mr. T.	18.0	Cholecystitis.
75	Mrs. P.	8.0	Hepatitis and appendicitis.
79	Mr. G.	13.8	Hepatitis and duodenal ulcer.
85	J. P. C.	18.0	Hepatitis and colitis.
89	Mr. O.	10.0	Amebic hepatitis.
90	R. P.	22.5	Cholecystitis.
92	Mrs. A.	7.5	Hepatitis and colitis.
93	Mr. Z.	13.8	Hepatitis and gall bladder.
94	Mr. T.	15.0	Hepatitis.
96	Mrs. B.	8.4	Hepatitis and duodenal ulcer.
97	Mrs. B.	7.5	Hepatitis and iritis.
98	Mrs. D. B.	15.0	Hepatitis and cholecystitis.
100	Miss H.	18.0	Hepatitis and cholecystitis.
101	Miss P.	22.0	Hepatitis and cholecystitis.
102	Mrs. B.	7.0	Hepatitis and cholecystitis.
104	Mr. W.	8.6	Myocarditis.
105	Mrs. L.	10.0	Hepatitis.
108	Mr. B.	15.0	Hepatitis and cholecystitis.
109	Mrs. N. R. W.	16.0	Hepatitis and cholecystitis.
110	Mrs. G. O. M.	10.0	Liver abscess.
111	Mr. N.	22.5	Hepatitis and iritis.
112	Mrs. P.	10.0	Hepatitis and enteritis.
115	Mr. O. M. T.	16.0	Hepatitis and gall bladder.
116	Mrs. S.	10.0	Hepatitis and fibroid.
117	Mr. P.	30.0	Cholecystitis.
118	Mr. H.	15.0	Hepatitis and iritis.
119	L. M. D.	6.0	Hepatitis and gall stones.

Of 43 nonoperative cases whose symptomatology, history and physical findings did not point to liver disease the average index was 5.8. The average here was increased by a few cases having more than usual colon symptoms.

TABLE VII.—NONOPERATED CASES IN WHICH NO HEPATIC OR GALL-BLADDER DISEASE IS SUSPECTED.

No.	Name.	Index.	Diagnosis.
29	Mrs. L.	6.2	Arthritis and appendicitis.
30	Mrs. F.	3.4	Arthritis and appendicitis.
34	Mrs. M. C.	5.2	Tuberculosis.
35	Mrs. C.	5.6	Chronic bronchitis and colitis.
44	Mr. H.	8.6	Chronic appendicitis.
45	Mrs. M. L.	10.0	Chronic colitis.
47	Miss C.	7.5	Colitis.
48	Mr. A.	7.5	Gastric ulcer.
50	Mrs. R.	5.0	Chronic appendicitis.
51	Mrs. S.	5.2	Chronic colitis.
52	Mrs. T.	4.0	Chronic colitis.
53	E. T. D.	5.0	Lues.
54	J. M. S.	4.0	Lues.
56	Miss Bl.	6.0	Chronic appendicitis.
57	Miss B.	7.5	Colon stasis.
59	Mrs. M.	5.0	Chronic colitis.
60	Mr. J.	5.0	Gastric ulcer.
64	Mrs. B.	3.0	Psychosis and colitis.
65	Mrs. Z.	3.3	Colitis and hypertonia.
66	Mr. R.	7.0	Pulmonary tuberculosis.
72	Mrs. I.	5.2	Iritis and colitis.
73	Mr. S.	8.0	Enteritis.
74	Mr. M. N.	5.2	Duodenal ulcer.
76	Mrs. H.	6.0	Enterocolitis.
77	Mrs. H.	3.0	Iritis.
78	Mrs. H.	7.5	Duodenal ulcer.
80	G. O. M.	5.0	Otitis.
81	Mr. W.	6.0	Lead poisoning.
82	Mr. H.	5.0	Gastric ulcer.
83	Mrs. B. P.	6.2	Appendicitis and arthritis.
84	Mr. B.	5.0	Arthritis.
86	Miss S.	6.5	Amœbic colitis.
87	Mrs. M.	6.4	Amœbic colitis.
88	Mr. B.	6.0	Enterocolitis.
91	Mrs. W. S. B.	4.0	Arthritis.
95	Mrs. Ph.	7.5	Arthritis.
99	Miss C.	9.0	Appendicitis.
103	Mrs. H.	6.0	Asthma and colitis.
106	Mrs. J. S.	6.0	Enterocolitis.
107	Mrs. M.	6.0	Chronic appendicitis.
113	Mrs. B.	3.0	Appendicitis.
114	Mrs. J.	7.5	Enterocolitis.
120	R. W.	6.0	Constipation and amœbiasis.

Two cases deserve to be reported more in detail.

Case Reports.—CASE I. Mrs. M. A., gave the usual gall bladder complaint of pain and distress. Physical examination showed tenderness in both cecum and gall bladder regions. The roentgen-ray examination was negative for stone, but gave a positive path-

ological gall bladder shadow. There was a cecal stasis of more than seventy-two hours. The stool examination showed *Amœba dysenteriae*. The urine was negative and the phenolsulphonephthalein elimination was 50 per cent. The first blood count showed a hemoglobin of 82 per cent; red cells, 4,290,000; white cells, 5600; neutrophils, 50 per cent; mononuclears, 43 per cent; transitionals, 7 per cent. The icterus index on June 18, 1924 was 13; on September 2, 1924, it was 10; only March 18, 1925, it was 10. A slight attack of the old trouble brought the patient to operation in April, 1924, at which time the index was 13 again. The operative findings were: A chronic cholecystitis with stone; chronic appendicitis with colon adhesions. The gall bladder was drained and the drainage was very black and profuse. At the end of the first week, the index had dropped to 8; and on leaving the hospital three weeks later, it had made a further drop to 6.4. The proven and undoubted diagnosis here was a cholecystitis, cholelithiasis, chronic appendicitis with colon stasis and adhesions; chronic amoebiasis (undoubtedly arrested) and chronic hepatitis. The clinical factor here most probably causing the hepatitis was the cholecystitis for this was the only active process, but by operative treatment the condition could be relieved. Since operation, the patient's return to normal has been excellent.

CASE II.—Mr. M. came with the complaint of intermittent unconscious spells, at times accompanied by convulsions. There was marked tiredness. He had a high degree of constipation and intestinal gas. The physical examination showed a blood pressure of 100 systolic and 60 diastolic. There was a marked dermatitis herpetiformis. The heart showed a slight systolic murmur. The laboratory findings were: Hemoglobin, 90 per cent; red cells, 5,100,000; white cells, 6100; neutrophils, 58 per cent; mononuclears, 42 per cent. The urine was negative, with a phthalein elimination of 60 per cent; the icterus index was then 11.5; the Wassermann test was negative; the nonprotein nitrogen was normal; roentgen-ray showed a chronic appendicitis with cecal adhesions and a pathological gall bladder. Before operation the index was 10. Twenty-four hours postoperative, it rose to 13.5. On the afternoon of the second postoperative day he was transfused. During the night following he almost died from heart failure, but was finally stimulated through until morning. His condition was that of severe shock. At that time his index reading was 39.5. After four or five days, the index again returned to around 10 and there was no more heart disturbance. His convalescence has been slow, but steady, and his index is now down to around 7. In this case, one could almost follow his clinical history by the curve of the icterus index.

Conclusions. We believe the following conclusions are justifiable:

1. The icterus index is the test of choice for the quantitative estimation of bilirubinemia for the reason that it is simple, accurate, and of definite clinical value.

2. There is no untoward effect or danger to the patient in its use.

3. The Widal hemoclastic crisis probably tests the proteopexic function of the liver, which is allied to, but different from, the bile forming function.

4. Liver function is probably closely associated with the behavior of the blood stream leukocytes. Both of these come under the influence of any foreign protein introduced either through the intestinal tract or through the tissues elsewhere. It seems to us probable that our leukocyte tests of today may be in reality liver-function tests. Extreme leukocytosis in the presence of bile is probably the result of a high grade hemopoietic stimulant acting not because of the presence of bile, but in spite of it.

5. The icterus index is in the last analysis, a measure of bilirubin in the blood stream. Its clinical interpretation must depend on all the factors that will produce this condition. It is a valuable aid in diagnosis, prognosis and treatment. The test is neither infallible nor specific in the diagnosis of any one disease, but as other clinical tests are rated, this one has a high marking.

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MITRAL STENOSIS AFTER THE FIFTH DECADE OF LIFE.

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It is currently believed that mitral stenosis is a serious valvular lesion, which entails a grave prognosis, and predicates a lethal outcome before early middle age. Such at least is the teaching in most text books. Robinson,¹ in Nelson's system, places the average age at death as thirty-five years. Most authors refer to the studies of Samways,² who, on analysis of 196 necropsies of patients with mitral stenosis found the average age at death to be thirty-eight years, of Duckworth,³ who reported this lesion as unusual after the age of forty-five and of Gillespie,⁴ who, from a study of the records of the Edinburgh Hospital, placed the average age at death in the fourth decade for men and in the fifth for women.

We have been impressed at Montefiore Hospital with the frequency of mitral stenosis in patients who are over fifty years of age, and in order to obtain a more accurate idea of the incidence of this valve lesion at a relatively advanced age, we have studied the records of all patients who were discharged during the last three years with the diagnosis of mitral stenosis. Very many of these were under our personal care during their stay in the hospital.

Montefiore Hospital is a hospital for chronic diseases, that is, it admits as patients individuals of all ages whose disability is such that a prolonged period of hospitalization extending over many months is necessary. Consequently, the patients are selected to a certain extent. Patients with heart disease, for instance, are usually those endowed with a very poor cardiac reserve, as a result of long standing cardiac disability. Early cases are not seen, as a rule.

During the last two and a half years 183 patients of all ages, including children, were discharged from or died at Montefiore Hospital with the diagnosis of mitral stenosis. Of these, 46, or exactly one-quarter, were over fifty years of age. The average age of this group was 57.7 years, and the oldest patient was eighty-three years. Every one of these cases was well authenticated. A careful search of the literature reveals further evidence that mitral stenosis is not so rare at an advanced age. Thus Mackenzie, in his book on *Diseases of the Heart*, states that patients with a non-progressive mitral stenosis may reach old age without symptoms.

Gillespie⁴ tabulates the age distribution of 535 cases of mitral stenosis as follows:

Ages.	Male.	Female.	Total.
1 to 9	9	4	13
10 to 19	41	72	113
20 to 29	49	95	144
30 to 39	55	57	112
40 to 49	35	28	63
50 to 69	64	24	88
69 plus	2	0	2
	<hr/> 255	<hr/> 280	<hr/> 535

Thus 16.8 per cent were over fifty years of age. Samways² found 10 per cent of 196 patients who were over sixty, and Wilson,⁵ 8 per cent of 62 cases and Cabot⁶ 23 per cent of 200 cases over fifty. There is enough evidence in the literature, therefore, in addition to our own findings, to indicate that mitral stenosis is not uncommon in the older age periods.

In a study such as this, one precaution in particular must be observed. In certain patients with large hearts, consequent usually on adhesive pericarditis or on hypertension, a presystolic murmur may be heard at the apex, although on autopsy no narrowing of the mitral orifice is found.⁷ These cases, however, are not very common and can usually be differentiated by the absence of the characteristic small pulse of mitral stenosis, of the cyanotic mitral facies, and of the sharply accentuated pulmonic second sound.

It is a matter of considerable interest to determine the cause of the valvular disease in these older individuals, but such an attempt is fraught with many difficulties. Even in the young, cases of mitral stenosis, as well as of other valvular lesions, are seen with considerable frequency, in whom it is impossible to determine the etiologic agent. It is generally accepted that from 60 to 70 per cent of patients with chronic valvular disease give a history of some previous rheumatic infection. In the remainder the cause of the valvular lesion usually remains a matter for speculation. If such a situation obtains in the younger age groups in whom memory is not yet dimmed by the lapse of time, it is evident that in elderly persons the number who can assign a definite cause for their heart disease will be still smaller; for, with the passing years, the recollection of minor illnesses becomes increasingly hazy.

It is not astonishing, therefore, that of our 46 patients only 17, or 37 per cent, gave a clear history of a typical rheumatic infection. We have classed 3 additional cases with the definite rheumatic group because of the fact that they evidenced aortic as well as mitral lesions, and in 1 case an adhesive pericarditis, and because 2 of them on necropsy presented typical healed verrucæ. Thus 20 of the 46 cases may safely be assigned to the rheumatic category.

In the group of mitral stenosis of undetermined etiology, we have

placed 12 patients who remembered no rheumatic infections, but who corresponded in their clinical manifestations to those discussed in the previous paragraph. They were, with one exception, under sixty years of age, were well nourished, with the typical mitral stenosis facies and a tendency to a plethoric appearance. In the case of many of these, were an accurate history obtainable, one would undoubtedly find indications of mild rheumatic episodes in childhood or in early adult life.

Finally, there is a group of patients who, with one exception, were over sixty years of age, in whom, too, there was no history of antecedent infections, but who, in addition to the physical signs of mitral stenosis, gave evidence of widespread arteriosclerosis of both peripheral and central vessels. These patients, as a rule, did not present the typical full-blooded appearance of the ordinary mitral patient, but were more poorly nourished and of a more sallow complexion. In them various complications, such as cerebral hemorrhage, cerebrospinal arteriosclerosis and diabetes, occurred. We have ventured to diagnose these cases as atherosclerotic mitral stenosis. We are well aware that a number of them might with propriety be placed in the "undetermined class," but we believe that the existence of an atherosclerotic form of mitral stenosis is sufficiently well established to warrant this classification, and to justify drawing attention to its frequency.

Huchard,⁸ some thirty years ago, was the first to describe this type of mitral stenosis, which he called "*le rétrécissement mitral des arterioscléreux*." He distinguished two forms: (1) An atherosclerosis implanted on an ordinary mitral stenosis; (2) a primary atherosclerotic mitral stenosis. He believed that in these cases the degree of narrowing of the valve was less than in the endocarditic type, and that the aperture, instead of being funnel, or buttonhole shaped, was more irregular, and in the figure of a cross or of an hour glass. In his usual didactic manner he built up a complete symptomatology about this lesion, and pointed out that the characteristic clinical picture was often masked by the associated presence of hypertension in the greater circulation. Some years earlier Pitt⁹ had published a paper on the association of granular kidneys with mitral stenosis, and had shown that in many instances both lesions were found in the same individual. The average age at death of his cases was fifty-two years for men and forty-two for women. Some years ago Cowan and Fleming¹⁰ reinvestigated this relationship between renal fibrosis and mitral disease and found a close correlation between the two. Their findings are not pertinent to the question we are discussing for they included both mitral stenosis and mitral insufficiency in one table. That atherosclerotic mitral disease associated with mitral insufficiency is common in patients with hypertension and nephrosclerosis is common knowledge. Their assumption, however, that in patients with mitral stenosis

who give no history of antecedent infectious disease, either atherosclerosis or chronic nephritis, is the cause of the heart lesion, is supported by insufficient evidence. Indeed, the relatively young ages of their patients and the well-known insidious progress of rheumatic infection speak against this view.

More recent writers have minimized the importance of atherosclerosis as a factor causing mitral stenosis.¹¹ Anitschkow,¹² indeed, on the basis of pathologic studies, reaches the conclusion that atherosclerosis can produce no deformity of the heart valves, but can only increase their rigidity to some extent. He believes that the fatty degeneration and calcification seen in distorted valves is a secondary change following necrosis of an old inflamed area. His reasoning does not seem quite sound, when one recalls the great ulcerations and deformities that are seen so frequently in the aorta consequent solely on atherosclerosis.

Many pathologic studies of atherosclerosis of the heart valves have been made and several types have been distinguished. The opaque yellow flecks of atheroma on the ventricular surface of the aortic leaflet of the mitral valve have been well described by Beitzke.¹³ These rarely, if ever, are of sufficient extent to produce the picture of clinical valvular disease. More significant is the same disease process when it is localized at the site of insertion of the mitral valve in the fibrous auriculoventricular ring and in the ring itself. Here the sequence of deposits of fat and cholesterol crystals, followed by calcification is very common, and leads to a typical pathologic picture which Dewitzky¹⁴ named annular sclerosis. In the advanced stages of this annular sclerosis large calcified nodules and strands are formed which may project into the lumen of the mitral orifice. At times there is secondary bone formation. The development of a complete calcified ring narrowing the mitral orifice is rare.¹⁵ At times this process by impinging on the bundle of His may injure it and so produce heart block.

Two of our patients who came to necropsy illustrate very well the manner in which atherosclerosis may cause mitral stenosis. As is apparent in Fig. 1, the significant lesion is the complete nodular calcification of the mitral ring which definitely narrows the auriculoventricular orifice; but to a lesser degree than does the typical endocarditic form of mitral stenosis. The mitral leaflets are thickened and sclerotic but not fused. The pathologic picture is not so clear cut in most cases, for combination forms of atherosclerosis superimposed on infectious valvular disease are common, so that it may be impossible to classify the lesion from the point of view of its etiology.

Since there is this difficulty in distinguishing the nature of the valvular disease at the autopsy table, it is not astonishing that in the clinic one often is unable to decide in the individual case whether a pure atherosclerosis or an old endocarditis has determined the

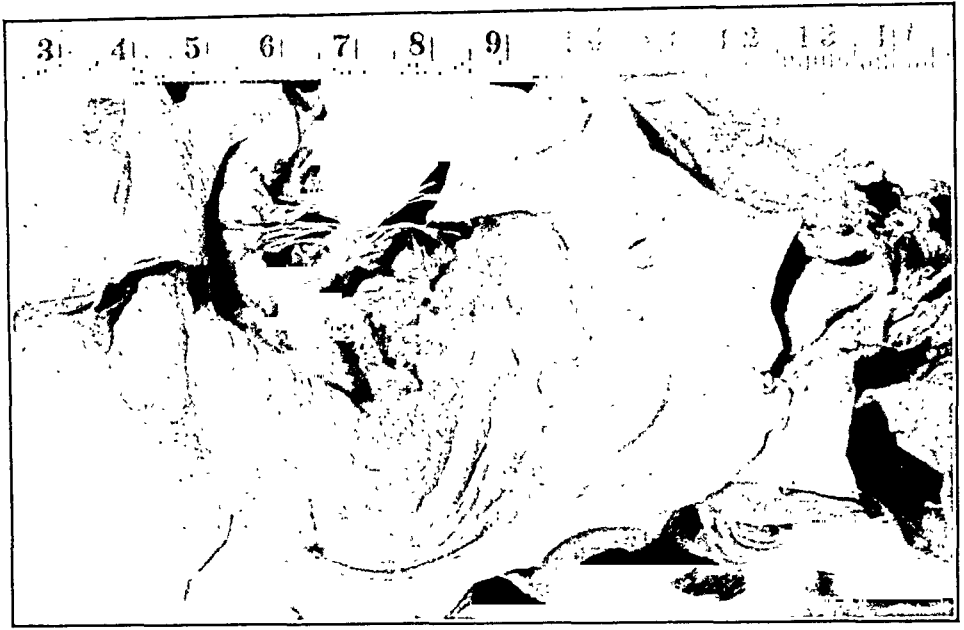


FIG. 1.—Arteriosclerotic mitral stenosis: Nodular calcification of annulus fibrosus.

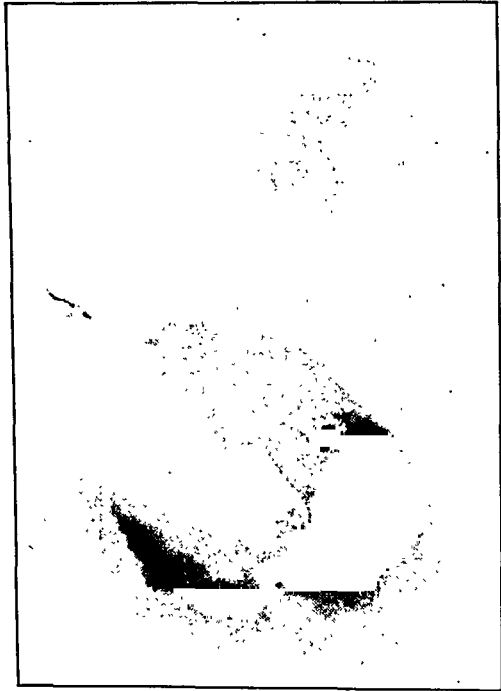


FIG. 2.—Roentgen-ray picture of auriculoventricular ring of Fig. 1.

lesion. The following diagnostic features, which, however, cannot be considered absolute, are characteristic of atherosclerotic mitral stenosis: (1) The absence of a history of rheumatic infection, or of another infection that might be considered as the pathogenic agent; (2) evidences of advanced arteriosclerosis in the peripheral or visceral arteries; (3) generally a poor nutrition and a sallow nonplethoric appearance; (4) complications ordinarily associated with arteriosclerosis; (5) an advanced age—usually beyond sixty.

The mistakes that may enter in such a diagnosis are manifold. As is apparent from the table, a negative history is no proof that no rheumatic infection has been experienced. Two of our patients classed as arteriosclerotic had had bronchiectasis for many years, 1 for ten and 1 for twenty-two years. It is impossible to determine whether or not this served as a source of infection of the valve. The presence of arteriosclerosis in one region of the body can be taken in only the most general way as evidence of a similar change in other vascular structures. Moreover, it is always possible that atherosclerosis may develop independently in a person with an endocarditic mitral stenosis. The age of the patient is a more or less arbitrary criterion which may result in placing survivors of the rheumatic group in the atherosclerotic category. The preponderance of females over males among our patients in the proportion of almost 2 to 1 corresponds to the sex distribution in the younger age groups. Were atherosclerosis a very frequent factor, one would expect men to exceed the women in numbers.

Of 147 patients of all ages with mitral stenosis, the auricles were fibrillating in 75, or over 50 per cent. In the series of patients over fifty years of age, 26 or 56.5 per cent were accompanied by auricular fibrillation. However, only 36 per cent of the atherosclerotic group, in contrast to 70 per cent of the rheumatic group, had this complication. The incidence of an elevated blood pressure is difficult to evaluate because of the limited number of cases. Hypertension, however, seems more common in the atherosclerotic form of the disease.

The study of this group of elderly patients with mitral stenosis reveals a number of other interesting facts. The 30 women had given birth to 119 children, or an average of almost 4 children to a woman. Only 6 of the women had no children, while 2 had 10 and 1 had 12 offspring. From the histories one cannot determine the age at which the heart lesion actually developed, for these patients characteristically manifested no symptoms until they were well past middle age. Many of the rheumatic group, however, told of attacks of arthritis in childhood or in early adult life, so that it seems probable that in many instances the mitral stenosis was well established during the childbearing period, and that the women underwent repeated pregnancies without cardiac distress.

TABLE I.—MITRAL STENOSIS IN PATIENTS OVER FIFTY.

Case number.	Sex.	Age.	Number of children.	Auricular fibrillation.	Blood pressure.	History.	Duration of cardiac symptoms in years.	Notes.
						RHEUMATIC MITRAL STENOSIS.		
8,129	F	55	0	—	110/60	Arthritis at 18	20	Died; aortic stenosis and regurgitation
8,242	F	57	1	+	150/88	Arthritis in childhood	2	Died
8,822	F	56	6	+	214/114	Arthritis, tonsillitis	14	Died; necropsy; tricuspid stenosis; granular kidneys
9,709	F	51	3	—		Subacute arthritis on admission	10	
9,780	F	52	3	+	90/60	Arthritis at 50.	2	
10,069	F	54	3	—	130/60	Arthritis from 24 to 34	3	Aortic insufficiency, diabetes
10,110	F	50	5	+	130/70	Arthritis at 31 and 37	1	
10,294	F	52	0	+		Arthritis from childhood to 46	2	Aortic stenosis and insufficiency
10,545	F	55	12	+	145/60	Arthritis at 48; tonsillitis at 22	7	
11,695	F	55	3	+	130/90	Arthritis at 47	7	
10,683	F	53	7	+	230/120	Many sore throats; "rheumatism" at 37	10	Aortic stenosis and insufficiency; bronchiectasis
11,245	F	55	5	—	180/100	Sore throat, rheumatism, chorea at 15	1	Moderate sclerosis of radials
8,482	M	56		+	140/80	Arthritis at 44	11	Spondylitis; diabetes
8,000R	M	56		—	110/60	Negative	25?	Died; necropsy: general arteriosclerosis; cardiac thrombosis
9,557R	M	52		+	144/90	Rheumatism at 12	7	Died; necropsy; adherent pericardium, aortic insufficiency, verrucous endocarditis
9,449	M	54		+	120/70	Negative	4	Embolism left brachial artery
								Died; aortic and tricuspid insufficiency

Case No.	Sex	Age	Mitral Stenosis	Mitral Stenosis of Undetermined Origin	Arteriosclerotic Mitral Stenosis	Notes
9,755	M	51	+	Arthritis at 41 and 49	1	Died; necropsy; healed verrucae on mitral and pulmonary valves
10,636	M	56	+	Arthritis at 25 Polyarthritis at 7	5	Died; necropsy; mitral ring calcified; radials and coronaries sclerosed; Streptococcus viridans infection of valves
11,118	M	52	+	122/85 110/60	1	Hemiplegia
9,279	M	64	+	130/70 145/90	15	Adenoma of thyroid Died; aortic insufficiency; Endometritis after second childbirth
8,105	F	52	+	160/85 176/90	2	Aortic insufficiency
8,909	F	50	+	146/80 186/98	1	Died
9,236R	F	55	+	138/76 140/76	1	Hemiplegia
9,621R	F	56	+	118/70 208/70	1	Arteriosclerosis; radials and temporals
9,926	F	54	+	118/70 208/70	1	Gastric ulcer
10,102	F	56	+	118/70 208/70	1	Hemiplegia; aortic insufficiency; sclerosis of radials
10,267	F	64	+	118/70 208/70	1	Died; necropsy; mitral ring calcified, leaflets thick and sclerotic, chordae shortened; cerebrospinal arteriosclerosis
10,433	F	53	+	118/70 208/70	1	
10,469	F	58	+	118/70 208/70	1	
8,888	M	53	+	118/70 208/70	1	
10,247	M	59	+	118/70 208/70	1	
11,363	M	53	+	118/70 208/70	1	
9,330	F	83	-	210/130	1	

TABLE I.—MITRAL STENOSIS IN PATIENTS OVER FIFTY.—(Continued.)

Case number.	Sex.	Age.	Number of children.	Auricular fibrillation.	Blood pressure.	History.	Duration of cardiac symptoms in years.	Notes.
			ARTERIOSCLEROTIC MITRAL STENOSIS.—(Continued.)					
10,527	F	60	0	+	145/80	Negative	4	Died; diabetes; arteries thick and tortuous
11,063	F	65	7	—	135/80	Bronchiectasis, 10 years	1	Bronchiectasis
11,125	F	66	2	—	130/75	Negative	1	Died; great emaciation; radial sclerosis
11,205	F	61	7	—	110/76	Pneumonia at 38; bronchiectasis	0	Examined twelve years ago; heart normal; eleven years ago systolic murmur with cardiac enlargement
10,332	F	68	5	—	180/110	Negative	0	Hemiplegia; arteriosclerosis
10,537	F	62	3	+		Negative	½	Poor nutrition; radials sclerosed
9,049	F	54	1	+	155/70	Negative	4	Obese; angina pectoris
12,024	F	60	7	—	120/64	Negative	½	Died; radials thick and tortuous; several apoplectic strokes
8,855	M	68		—	160/70	Negative	2	Arteries sclerotic; bundle branch block
10,642	M	61		+	150/60	Negative	6	Four years ago had simple mitral insufficiency; sclerosis of radials
10,772	M	62		+	184/100	Negative	5	Hypertension five years; general arteriosclerosis
11,119	M	69		—	138/90	Negative	0	Died; carcinoma of stomach; marked arteriosclerosis
11,136	M	68		—	100/66	Negative	10	Died; necropsy; mitral ring calcified; leaflets thick and calcified

As is apparent from Table I, in most instances many years elapsed between the attack of arthritis and the present symptoms of heart disease. The most striking case is that of a man sixty-four years of age, who had had an attack of polyarthritis when he was seven years old, and none subsequently.

TABLE II.

	Rheumatic.	Undetermined.	Arterio-sclerotic.	Total.
Number of cases	20	12	14	46
Age range in years	50 to 64	50 to 64	54 to 83	
Average age in years	54.4	55.1	64.8	57.7
Sex:				
Male	8	3	5	16
Female	12	9	9	30
Auricular fibrillation:				
Number	14	7	5	26
Per cent	70	58	36	56.5
Diastolic blood pressure over				
90	3	1	3	7
Systolic blood pressure over				
140	6	6	7	21

Summary. Mitral stenosis is not uncommon in the sixth and seventh decades of life. In most instances it is the end result of a rheumatic infection in childhood or early adult life. The mitral narrowing is not extreme, and the lesion is nonprogressive, or very slowly progressive, so that significant symptoms do not develop for many years. Women with such a condition may apparently undergo many pregnancies without distress and without injury to the heart.

In a certain number of cases of mitral stenosis in elderly persons, the valvular lesion cannot be interpreted as the end result of an ancient endocarditis, but must be regarded as a primary atherosclerosis of the mitral valve, and particularly of the auriculo-ventricular ring. The characteristic pathologic finding is a widespread calcification of the mitral ring encroaching on the lumen of the auriculoventricular opening with thickening and at times calcification and fusion of the valve cusps.

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ATYPICAL TABES DORSALIS (FORME FRUSTE): SURGICAL ERRORS IN, WITH LEADING POINTS IN DIAGNOSIS.*

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THE purpose of this paper is to point out some mistakes that are made in the diagnosis of the incomplete or atypical form of tabes dorsalis. These mistakes at times lead to needless surgical operations. It is also my purpose to illustrate with a case report, facts long recognized in neurological circles, but at times overlooked in general medical and surgical fields.

It is now over fifty years since Charcot first linked up gastric crises with tabes dorsalis as a cause of acute abdominal distress and emphasized the fact that preataxic crises may occur years before locomotor trouble. He also described the "forme fruste" or atypical type with this condition. Even with improved methods of study and diagnosis of our cases, we still see far too numerous mistakes. Some of the reasons for these errors are: (1) That the cases usually having crises are not typical. Many cases, probably one-half, deviate from the text-book picture of tabes dorsalis, which any layman can recognize in the end-stages as locomotor ataxia. The cases differ either by the presence of rare symptoms or the symbiosis of other associated diseases. (2) We fail to make a correct interpretation of the case because too often the disease is not looked for. Hurried histories, incomplete examinations particularly neglecting the nervous system and a failure to remember that the root pains of cerebrospinal syphilis may simulate almost any abdominal lesion, account for many errors. (3) In doubtful cases spinal fluid examinations are not resorted to frequently enough. A few physi-

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cians are still under the impression that a negative blood Wassermann test rules out neurosyphilis, of course we now know this is not true. In some of these doubtful cases an exploratory laparotomy has been done where a spinal puncture might have settled the diagnosis. In a small percentage of cases the spinal fluid examination will not clinch the diagnosis as illustrated in my case, but in the large majority of instances this examination would settle the question.

The following case report presents many interesting facts in the ten-year course of the disease. Records were obtained from the various hospitals in which the patient received five major abdominal operations.

Case Report. Mr. J. T., aged forty-four years, first came under my observation at the Philadelphia General Hospital, April 5, 1923. He complained of attacks of pain in the abdomen, with vomiting. At nineteen years of age he contracted a chancre and received six weeks of treatment. He had no secondary eruption. In 1912 he began having attacks of sharp cutting shooting pains in the back, abdomen and legs accompanied by vomiting. These attacks at times lasted two weeks, recurring at intervals of four to five weeks. In July, 1913, he was admitted to a well-known Philadelphia hospital for an exploratory laparotomy. The surgeon found the stomach normal; no masses, pylorus normal, the liver smaller than normal with many small nodules, "hob nailed," and gall bladder normal. The appendix was retrocecal but apparently normal. The diagnosis was cirrhosis of the liver. He was discharged in six weeks only to return one week later with an attack of pain and vomiting. Another surgeon advised operation and this time a posterior gastroenterostomy was done. The liver was found cirrhotic and there were a few adhesions about the pylorus. The abdominal organs were otherwise normal. He continued to have the same attacks at irregular intervals, returning to this hospital off and on until August, 1921, when a third operation was performed, which was advised against by the surgeon but insisted upon by the patient. This incision was over the gall bladder. Multiple adhesions were found and the abdomen was closed without interference. It should be stated now that in addition to his attacks of pain and vomiting since 1918 he had urgency, precipitancy and dribbling of urination. Since 1920 he had lost his sexual power. Following his third operation the attacks persisted and in June, 1922, he was admitted to another hospital on the service of a well-known surgeon.

Here another exploratory operation was performed; innumerable adhesions were found and after working for two hours the surgeon abandoned the operation. In two weeks the same old attacks returned and were only relieved by morphin.

In September, 1922, he was readmitted, on another well-known

surgeon's service, because of persistent vomiting. At this time a very complete study was made from a general physical and laboratory standpoint, but no mention was made of the nervous system. His general physical status was essentially negative as were all laboratory tests including a blood Wassermann. The gastro-intestinal study revealed a marked stasis in the ileum and a gastro-jejunal ulcer was considered. The surgeon who later reported the case states in his report: "The patient begged me every day to operate on him, I kept him in the ward long enough before the operation to be sure that he really was suffering and not merely neurasthenic." He felt the trouble was due to a vicious circle in his former gastroenterostomy. At the fifth operation he also found adhesions everywhere and with difficulty dissected the jejunum from adhesions, found no ulcer, but the duodenal loop was obstructed so the old anastomosis between the jejunum and stomach was separated. Four days after this operation the patient again vomited. More roentgen-ray studies were made, all efforts were focused on finding a cause within the abdomen; the possibility of root pains seems not to have been considered. The surgeon's further report is interesting because of his interpretation of the case: "The only criticism that I think I could make in addition to condemning the unnecessary operations which have been done upon him is that he has never had his appendix removed and perhaps I should have done it myself, but he had enough trouble when he was under my care to make me willing to postpone that for another occasion."

The patient continued to have his attacks before and after admission to the Philadelphia General Hospital. A complete neurological study revealed the following facts: Inequality of the pupils with the right pupil reacting slower to light than accommodation, diminished pain sense over the left lower thoracic region and over the left leg below the knee. The knee jerks were both active; the right Achilles was absent and the left was subnormal with hypotonia of the leg muscles; there was no ataxia. A cystoscopic examination revealed a relaxed vesical sphincter; the musculature looked like that seen in tabetic bladders, and the posterior urethra was anesthetic. The urologist stated the urinary frequency and urgency was entirely due to failure of proper innervation of the bladder musculature. Complete laboratory studies, including gastric analysis, blood chemistry and gastro-intestinal roentgen-ray were essentially negative. Two blood and spinal fluid Wassermann tests were negative. A diagnosis of atypical tabes with involvement of the thoracic and sacral segments was made, but not sufficient lumbar involvement to catch the patellar reflexes. He was given 16 neoarsphenamin injections and discharged in July, 1923.

The patient again came under my observation in September, 1923, at the Philadelphia Orthopedic Hospital and Infirmary for Nervous Diseases on the service of Dr. F. Sinkler. He gave the

same old complaint. Serological studies of the blood and spinal fluid were again entirely negative. The neurological status was the same as before except that he now showed a right-sided Babinski reflex. After several severe attacks of pain and vomiting he was given 4 Swift-Ellis intraspinal injections, after these he showed a bilateral Babinski. The blood Wassermann as always negative but a provocative reaction from the intraspinal injections produced a strongly positive spinal fluid Wassermann for the first time and gave a gold curve of 4554321000. The fluid a short time later became negative. He continued to have attacks of pain in the abdomen and legs usually accompanied by vomiting. Several times he had peculiar attacks of sudden unconsciousness in which he became pulseless and respirations ceased for about thirty seconds.¹ There was no convulsion and consciousness was regained in a few minutes. The patient had complete amnesia for the attacks. In view of his continued suffering without relief on vigorous treatment he was referred to Dr. F. C. Grant for section of his antero-lateral columns. On March 12, 1924, a bilateral chordotomy at the fifth thoracic segment was done. Following this his attacks ceased until September, 1924. He dragged his right foot some and showed pain and temperature disturbance as high as the third lumbar segment but no Babinski reflex was present. His pain reappeared in a single point 2 inches to the left of the umbilicus accompanied with vomiting. Trophic lesions developed in the form of punched out crateriform ulcers about the size of a quarter over the anterior surface of the thighs and shins. Intragluteal injections of mercury were given. Decubital ulcers formed at the site of the injections. In addition he developed an ulcerative cystitis and died November 30, 1924.

A necropsy limited to the brain and spinal cord revealed the following findings: The cerebral hemispheres showed a definite edema with flattening of the convolutions. The pia arachnoid was definitely milky and slightly thickened. The dura mater was slightly thickened. The spinal cord showed a distortion at the level of the operation and a definite thickening of the meninges to $\frac{1}{4}$ cm. was present over the posterior surface in the lower sections. Microscopic sections of the cord revealed much new connective tissue formation in the lateral parts of the cord at the site of operation. Complete degeneration was present in the cerebellar tracts. The posterior columns were only slightly affected. In one section a unilateral change was present in the column of Burdach. The anterior horn cells showed definite atrophy and degeneration.

Comment. The case requires but little comment since the story is clear and the findings positive. It should be said that no mention was made in the other hospital reports of a chancre history and it is possible the patient concealed this fact. It is indeed surprising that five different surgeons failed to consider a neurological disorder, when

after each operation he had not obtained relief from pain. The patient at various times begged for operations as they often do in the hope of relief, but this should not be sufficient excuse for surgery. From a neurological point of view the atypical findings of the disease are instructive. In twelve years there were no locomotor signs, only suggestive pupils, hypalgesia over the lower thoracic region and left leg, and one absent Achilles jerk. The serological studies which were repeatedly negative and only positive from provocative reaction illustrate the fact that a negative spinal fluid Wassermann does not rule out cerebrospinal infection in old or treated cases. The relief from pain obtained by section of the antero-lateral columns was instructive and should have been done years before instead of the other operative procedures. This operation is indicated in chronic cases where no relief is obtained from treatment and the suffering incapacitates the individual.

The incidence of gastric crises is given as occurring in 10 per cent of tabetics by Starr,² Holmes,³ Hall,⁴ and Leimbach.⁵ Lücke⁶ found 12 per cent of 250 cases had visceral crises. Bonar⁷ found 16.78 per cent of 286 cases had gastric crises, while Nuzum⁸ found in 1000 tabetics, crises occurring in 22 per cent. It is impossible to estimate from the sparse literature the frequency of operative mistakes in these cases. There are numerous scattered reports of isolated cases where from one to three operations were performed with no relief of symptoms; only to have the syphilitic etiology later proved and the patient's symptoms relieved by treatment. All the reported cases are by internists or neurologists and none are to be found in the surgical literature. Here one only finds occasional casual reference to the frequency of such mistakes. There are a few collections of cases from various clinics that give us some idea of the frequency of mistakes in surgical diagnosis in these cases.

Nuzum⁸ reviewed the records of 1000 tabetics from the neurological service of Cook County Hospital and found 97 needless laparotomies had been performed on 87 of these patients. Of these, diagnoses of gastric ulcer and gall-bladder disease were the most frequent, with the diagnosis of appendicitis a close third. Operations had also been performed for almost every other type of abdominal lesions. Several patients had been operated upon several times. After the first incision, postoperative adhesions seem to be a favorite excuse for having a second, third, fourth or even fifth "look in."

Woltman⁹ found from 120 patients having syphilitic gastric crises that 25.8 per cent had been subjected to unfruitful surgical interference and 61 operations had been performed in this group. The appendix was the most frequent supposed offender in his series, with the gall bladder second and the stomach third. The pelvic organs, kidney, colon, postoperative adhesions and in some cases exploratory laparotomy were given as diagnoses. It is surprising the number of instances in which repeated operations have been performed, on

the same patient, even after no pathological lesions were found in previous explorations, and the history obtained showed that no relief was experienced from previous operations. No suspicion that a neurological disorder might account for the symptoms ever seemed to have arisen, even after four or five surgical failures.

It is also interesting to find in these cases as well as in other reflex or functional nervous disorders how often postoperative adhesions are blamed when a correct diagnosis has not been made: Ziegler,¹⁰ in a study of 164 psychoneurotics, found 18.3 per cent had received one or more major abdominal operations for the relief of psychoneurotic symptoms, all without avail. No report was found of a tabetic having had more than five abdominal operations. Holmes reports a case that had five abdominal operations performed before a correct diagnosis of tabes was made. One patient in Nuzum's series had been subjected to five laparotomies with no relief of symptoms. The last three were made for postoperative adhesions. Woltman, Newburgh¹¹ and Tuohy¹² report cases upon whom four major abdominal operations had been performed before complete neurological and serological studies proved the correct etiology to be syphilitic radiculitis. In my case the five operative descriptions have been given.

Difficulties in diagnosis are not so marked in the well advanced ataxic patient, where we find the absent deep reflexes, Argyll-Robertson pupil, positive Romberg and other classical symptoms. The fact that the so-called typical pictures are the exception rather than the rule cause our difficulties. There is no one symptom that may not be absent. For example, we hear it said, tabes was ruled out because the knee jerks were present. The knee jerks may be normal; exaggerated in both; normal in one and diminished in the other or both absent. The reflex changes depend upon the location of the pathological process; so, for instance, unless the lesion extends to the fourth lumbar segment of the cord the knee jerk will be present. If the first sacral segment is not involved the Achilles jerk will be present. Also if there happens to be accompanying lateral column disease the reflexes may be exaggerated. The preataxic stages before extensive degeneration of the posterior columns occurs is the time in which most crises occur. This was true in my case, in which there was but slight posterior column degeneration. Crises may last for years (eighteen years according to Oppenheim¹³) without marked reflex alteration. As a matter of fact the knee jerks are not absent in over 75 per cent of early cases. Hall, for example, in 100 cases found them absent in but 65 per cent; present in 22 per cent; exaggerated in 4 per cent and unequal or sluggish in 6 per cent. Frey¹⁴ found them absent in 56.47 per cent of 850 cases. Collins¹⁵ reports 77 per cent of 140 cases had absent knee jerks in the preataxic stages and 84.3 per cent in the well advanced stages. Statistics from various clinics of large groups of

cases in the later stages show higher percentages with absent patellar reflexes. Thomas¹⁶ in 111 cases reports absent knee jerks in 81 per cent, Mendel and Tobias¹⁷ found them absent in 82 per cent, Lucke in 90 per cent, Leimbach in 92 per cent and Bonar reports 95 per cent of 286 cases had absent patellar jerks. Riley¹⁸ states 90 per cent of 61 cases had absent knee jerks. He also in another report¹⁹ gave 7 cases of tabes with knee jerks retained or exaggerated.

The same thing is true for the Argyll-Robertson pupil and Romberg's sign. These classical signs are present in only a little over one-half of the early cases. In such a disease with variable symptoms and signs we must take the picture as a whole to establish a diagnosis. The following combination of symptoms and signs in order of frequency would catch most cases. The history of onset with the development of the subjective sensations is important. The story of the lacerating pains as though shot, occurring irregularly, of momentary duration leaving behind an intensely sore spot is another. These pains may be the only complaint for several years with no objective neurological findings present except a positive spinal fluid. The paresthesias—a sense of numbness in the feet with a feeling as though walking on air or associated with an uncertainty in placing the feet without looking—or a girdle sensation about the abdomen, are usually early symptoms. Pupillary changes such as inequality, irregularity, with often a loss of the consensual reflex are present before the Argyll-Robertson pupil appears. The common chest-zone anesthesia, with loss of pain sense more marked than that of touch, also hypalgæsic areas over the face, thorax or extremities, are early findings. These patients early cannot recognize the vibration of a tuning-fork over the malleoli, patella or sacrum, or tell in what position the toes are placed. The loss of the normal muscle, testis, ulnar or Achilles tenderness from pinching is often striking. The Achilles jerks are often diminished, unequal or absent before the patellars. Many patients early in the disease complain of urgency, precipitancy or incontinence of urination and beginning impotence. Isolated cranial nerve palsies, eye symptoms (diplopia, ptosis) or primary optic atrophy may be early signs in certain cases. When the disease is well advanced there will usually be ataxia, Romberg's sign, and unequal, sluggish or absent knee jerks. These latter findings when present are of extreme value but their absence does not necessarily rule out tabes. To establish an absolute diagnosis in all cases of doubt, spinal serological studies should be done. An increased total protein content, pleocytosis and a positive Wassermann are generally present, remembering that in late tabes only 75 per cent are positive. A provocative reaction in negative cases will bring out more positives.

There are many facts lost through faulty technic in a neurological examination, especially the early changes. In studying pupils it is important to study contour, size and equality as well as taking

the consensual light reflex, because often there is a loss of response when the light is thrown on the opposite retina before the typical Argyll-Robertson phenomenon appears. Another important point in pupillary examination is to avoid the accommodation reflex in testing for light reaction, by having the patient focus on a distant object, then play the beam of light in from the side of the eye. The tuning-fork test and Achilles jerks are too frequently neglected. To obtain the Achilles jerks it is important to have the patient in a comfortable kneeling position with the gastrocnemius muscles relaxed.

Gastric crises may simulate any gastro-intestinal condition and may appear early in cerebrospinal syphilis, even being the sole complaint before any of the older signs of the disease are present. Even then they are fairly unique in their manifestations. They may be present either as pain or vomiting alone, or both together, which is more common. The onset is usually sudden with mid-line pain, without reference to meals or the character of food. The pains are dull or sharp, often shooting and of agonizing character associated with sialorrhea, extreme nausea and vomiting, and great prostration and lasting a few hours to several days. Then the pains cease abruptly, with surprisingly rapid recovery of the patient, only to recur again in a few days, weeks or months. During the attacks, while the abdomen may be hypersensitive to light touch, there is no deep tenderness to palpation and there is no muscular rigidity. The attacks are almost always afebrile; in rare instances there may be pyrexia but without leukocytosis. Often relief is obtained by a hypodermic of adrenalin and in gastric crises after adrenalin the blood pressure usually falls instead of being increased as in the normal reaction. In a differential diagnosis it should be remembered that crises are not always typical and do not always commence and end suddenly but may be present as vague gastric distress. The attacks with severe retching and vomiting without pain are particularly hard to determine. Intestinal, rectal and bladder crises also occur. It should not be forgotten that hematemesis may occur in crises, but of course this should excite suspicion of an organic lesion. Then the possibility of a coëxistent gastro-intestinal lesion with tabes such as gastric ulcer²⁰ should be kept in mind. The possibility of the unusual condition of syphilis of the stomach must also be considered.

This report is not given in the spirit of criticizing the surgeon who is unfortunate enough to operate upon such patients. He cannot be expected to be a neurologist and often these atypical cases are extremely difficult of diagnosis. For the patient's welfare and the surgeon's happiness he should study his patients carefully, especially those with recurrent abdominal attacks presenting scars from previous operations and these who give a history of "no relief" following previous operations or "nothing wrong was found." Whenever

in doubt it is far safer to have a complete neurological study and a spinal fluid examination made and more satisfactory in the end than having opened an abdomen by mistake.

Summary. Atypical or "forme fruste" type of tabes is the most frequently missed form of the disease. Gastric crises in this variety often lead to unnecessary abdominal operations.

Incomplete histories, careless examinations and infrequent spinal punctures in doubtful cases account for most errors. Gastric crises occur in from 10 to 20 per cent of all cases of tabes dorsalis.

Reliable reports indicate that more than 10 per cent of tabetics have needless operations performed at least once upon a mistaken diagnosis. There are frequent reports in the literature of patients having had four or five abdominal operations when the cause of the symptoms was root pains of syphilis.

The classical signs of tabes are absent in approximately one-half of the early cases, when abdominal pains may be present. The knee jerks are normal or exaggerated in at least 25 per cent of early cases. The same applies to ataxia, Argyll-Robertson phenomenon and other later signs. Approximately 10 per cent of cases remain atypical throughout the entire course of the disease.

A complete life story of the individual with a careful analysis of the onset and development, a careful neurological examination and a spinal fluid study should be made where there is the slightest doubt as to a diagnosis.

In patients presenting recurrent abdominal attacks with no relief from previous operations, the possibility of an atypical form of tabes dorsalis should be very firmly impressed upon the minds of surgeons, in order to decrease the all too frequent incidence of unnecessary operations upon tabetics.

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GLUCOSE TOLERANCE TESTS IN CHILDREN.

I. BASED ON BODY WEIGHT.

II. BASED ON NUTRITIONAL SURFACE AND BODY SURFACE.

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I. Based on Body Weight. The sugar tolerance of children between the ages of three and twelve years has not been as carefully studied as the tolerance of adults or infants. This work was undertaken with the expectation of establishing a standard test for normal children.

The children tested were in the children's surgical wards of Mt. Sinai Hospital. The majority were Jewish children of Russian parentage. These children were, as far as could be ascertained, in good health and had been admitted to the hospital for some surgical procedure such as inguinal hernia, internal strabismus, or some minor nose and throat operation. These children presumably had had no acute infection for several weeks before admission. These tests were done before the surgical procedure; if this was not possible, several weeks were permitted to elapse after operation. Eighty-four children in all were tested, 14 of whom were retested, making 98 tests in all. Seventy per cent of the children tested were males. This predominance of males was merely accidental.

The test was begun after an overnight fast of fourteen hours.

The children were kept in bed until the test was completed. Epstein's modification of the Benedict microchemical method for blood sugar was used, the 0.2 cc. of the blood being obtained by pricking the finger. Samples of blood were taken previous to the ingestion of the glucose, and thereafter every half hour for two hours, and a final sample three hours after ingestion of glucose, making 6 tests in all. No other food or water was permitted until the completion of the test. Picric acid was added at the time the sample was taken and the specimen kept in the ice box until analysed the same afternoon by one of us. Urine specimens were collected when possible at half-hour intervals for four hours.

Glucose was given in varying amounts ranging from 0.8 gm. to 3 gm. per kilo of body weight. The glucose was given in a 30 per cent solution to which a little lemon juice was added to make it more palatable. According to John,¹ this concentration of glucose has no special effect on the secretion of gastric juice or on the concentration of the blood. The glucose was weighed out the day before, the water being added just before ingestion. Pure anhydrous glucose was used, except in a few cases where granulated glucose was substituted. The latter was always analysed and due allowance made for impurities. It has been shown by Wang and Felsher² that the absorption curve of the pure and the granulated glucose is essentially the same.

In order to determine the tolerance of these children for varying amounts of glucose, regardless of age, they were divided into 3 groups as seen in Table I. The amount of glucose given to the children of Group II is comparable to that generally given to adults. Janney³ believed that 1.8 of glucose per kilo of body weight was the correct amount. Others advocate giving 100 gm. of glucose to all adults regardless of body weight. This would mean about 1.5 gm. of glucose per kilo of body weight in a normal individual weighing 68 kilos or 150 pounds.

TABLE I.—TOLERANCE BASED ON VARYING AMOUNTS OF GLUCOSE PER KILO BODY WEIGHT.

Group.	Glucose per kilo, gm.	End of 2 hours.			End of 3 hours.		
		Total cases.	Returned to fasting level.		Total cases.	Returned to fasting level.	
			Cases.	Per cent.		Cases.	Per cent.
Group I . . .	0.8 to 1.6	33	15	45	32	25	78
Group II . . .	1.7 to 1.9	19	5	31	19	17	89
Group III . . .	2.0 to 3.3	46	11	24	39	25	64

The tolerance of each group is recorded in Table I. The number and the percentage of cases in which the blood sugar returned to the fasting level at the end of two hours and at the end of three hours is recorded.* In Group I, 45 per cent of the cases returned to the fasting level within two hours. An additional 34 per cent returned to the fasting level within three hours, making a total of 79 per cent of this group returning to the fasting level within three hours. In Group II of this table it is shown that 31 per cent returned to the fasting level within two hours and an additional 58 per cent within three hours, a total of 89 per cent. In the third group 24 per cent reached the fasting level in two hours, and 40 per cent more in three hours, making a total of 64 per cent.

It appears, therefore, from these cases that in only about 83 per cent of normal children receiving less than 2 gm. of glucose per kilo of body weight, will the blood sugar return to the fasting level at the end of three hours. It is difficult to understand why the blood sugar of so large a percentage of children (17 per cent) does not return to the fasting level at the end of three hours. This delay may be due to the rate of absorption from the intestines, some individuals absorbing more slowly and therefore maintaining their blood sugar at a higher level for a longer period. John¹ believes, however, that this delay in absorption is of no great importance. On the other hand the power to convert and store excess glucose, in the form of glycogen, by the liver or the extraction of glucose from the blood by the tissues may not be so well developed in some children as others. This possible irregularity in absorption and storage may also account for the fact that the blood sugar in 60 to 80 per cent of adults⁴ returns to the fasting level in two hours, whereas it takes three hours in children. The factor which controls the removal of sugar from the blood stream has yet to be determined.

Previous workers have stated that the younger the child the better the glucose tolerance. This fact has been substantiated by our findings. The children were divided into 3 groups according to their ages as seen in Table II. Each group was then subdivided according to the amount of sugar given, namely, those children receiving less than 2 gm. per kilo of body weight and those receiving more than 2 gm. per kilo of body weight.

Table II shows that children of all ages receiving less than 2 gm. per kilo of body weight have about the same tolerance at the end of three hours: 73 per cent in the younger children and 77 per cent in the older children. However, when over 2 gm. of glucose per kilo of body weight were given, the younger child had an excellent tolerance, 96 per cent returning to the normal in three hours, whereas in the older group only 43 per cent returned to the normal.

* For practical purposes those cases whose blood sugar returned within 15 mgm. of the fasting level, were included in the total percentage.

TABLE II.—GLUCOSE TOLERANCE IN RELATION TO AGE AND AMOUNT OF GLUCOSE PER KILO BODY WEIGHT.

Age, years.	Glucose per kilo, gm.	End of 2 hours.			End of 3 hours.		
		Total cases.	Returned to fasting level.		Total cases.	Returned to fasting level.	
			Cases.	Per cent.		Cases.	Per cent.
3 to 6 {	1.5 to 1.9	16	7	44	16	12	73
	2.0 to 2.9	26	7	27	24	23	96
7 to 9 {	1.2 to 1.9	13	2	16	13	10	77
	2.0 to 3.3	10	0	0	7	2	28
10 to 13 {	0.8 to 1.9	23	10	43	23	18	78
	2.0 to 3.0	10	3	30	7	4	57

Special comment must be made of those children from seven to ten years of age receiving over 2 gm. of glucose per kilo of body weight. In 7 cases tested only 2 returned to the fasting level in three hours. None returned to the fasting level in two hours. The number of cases is too small from which to draw any conclusions. It would be of interest to study a large group between these ages in order to ascertain if there really is a decreased tolerance at this period of childhood.

TABLE III.—GLUCOSE TOLERANCE PER KILO BODY WEIGHT IN RELATION TO AGE, AMOUNT OF GLUCOSE, AND STATE OF NUTRITION.

Age, years.	Glucose per kilo, gm.	Variations from Baldwin- Wood standard, per cent.	End of 2 hours.			End of 3 hours.		
			Total cases.	Returned to fasting level.		Total cases.	Returned to fasting level.	
				Cases.	Per cent.		Cases.	Per cent.
3 to 6 {	<2 {	-7	2	2	100	2	2	100
		Normal	11	5	45	11	8	73
		+10	3	0	0	3	2	66
	>2 {	-7	5	1	20	4	3	75
		Normal	17	7	41	16	15	94
		+10	3	0	0	3	3	100
7 to 13 {	<2 {	-7	9	2	22	9	9	100
		Normal	18	6	33	17	14	82
		+10	12	4	33	11	5	45
	>2 {	-7	9	0	0	6	2	33
		Normal	8	2	25	7	3	42
		+10	1	0	0	0	0	0

To determine whether the carbohydrate tolerance is affected by the state of nutrition the children were grouped into 3 classes in accordance with the Baldwin-Wood Height, Weight, Age Tables as seen in Table III. Of the children from three to six years of age receiving less than 2 gm. of glucose per kilo of body weight, those classified as underweight seem to have a better tolerance than those classified as normal or overweight. When given more than 2 gm. of glucose, however, the tolerance seems to be the same regardless of the state of nutrition. The number of cases is yet too small to draw any definite conclusions. At the end of two hours many of the underweight and normal group had reached the fasting blood sugar level, but in none of the overweight children did this occur.

The tolerance for less than 2 gm. of glucose per kilo of body weight is good in children over six years of age whose state of nutrition is poor or normal. The tolerance for over 2 gm. of glucose per kilo of body weight of all older children is poor. No comparative study can be made in this group.

It is our impression, however, that the overweight children should not receive the same amount of glucose per kilo of body weight as the normal or underweight children. Apparently in the overweight child the glucose is not metabolized or withdrawn from the blood stream by the liver and other tissues as rapidly as in the normal or underweight child. There must be a difference in the general metabolism of such overweight children, as they often gain on a diet containing fewer calories than calculated from their basal metabolism.

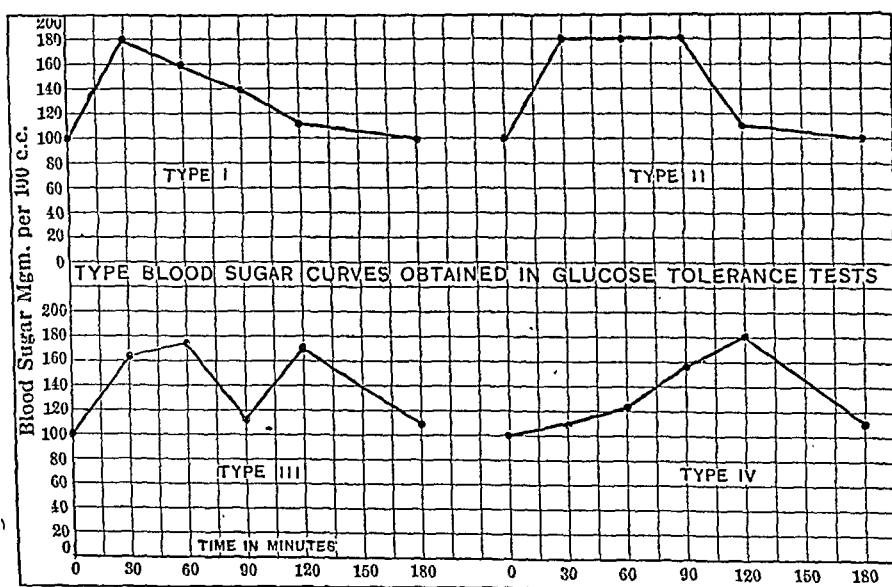


CHART I.

Four distinct blood-sugar curves were obtained by plotting the blood-sugar figures. In the majority of cases (70 per cent) the curve

rose rapidly to the maximum and at once began to fall to its original level. In 9 per cent of the cases the maximum level was sustained for a longer time, the so-called plateau curve. In 7 per cent of the cases the curve rose slowly reaching its maximum point at the end of ninety to one hundred and twenty minutes and then quickly falling to its original level. In 14 per cent of the cases the curve reached its maximum at the end of one hour, then fell but rose a second time making two peaks in the curve.

Many of these irregularities in the curves may be explained by the observations of Hansen⁵ on sugar-tolerance tests in adults. She showed that if the blood sugar is determined every two minutes for two hours the plotted curve is not smooth but that there are distinct oscillations, the blood sugar varying as much as 20 mg. from minute to minute, and that the greatest variations take place at the plateau portion of the curve. These oscillations may affect the accurate estimation of the highest and lowest points of the blood-sugar curve when blood-sugar determinations are made at thirty minute intervals. They would also explain the apparent but possibly not real differences in the blood-sugar curves of the same individual on two different days. Blood-sugar determinations taken every thirty minutes, however, give a fairly accurate picture of the true blood-sugar curve.

The blood sugar in the fasting state ranged from 90 mg. to 130 mg., the average being 108 mg. per 100 cc. of blood. This amount is in agreement with the findings of others who used the same method. A few of the children cried with fear while the blood was taken, a mental state which according to Folin and Berglund⁶ may cause a rise in the blood sugar. Hansen⁵ has shown, however, that the blood sugar of a normal fasting adult may vary 20 mg. within one hour's time.

After ingestion of glucose, the blood sugar reached its maximum height within an hour in 90 per cent of the cases as noted by other investigators. Although the average maximum was 180 mg. of glucose per 100 cc. of blood, nevertheless in 20 per cent of the cases it rose above 200 mg. This high level was reached, not only in cases where large amounts of sugar were given, but also in a few cases where small amounts were administered. The average maximum in the obese children was 190 mg. per 100 of blood as compared to 178 mg. in the normal and underweight. The blood sugar of children between seven and ten years of age reached a higher average level than those younger than seven and older than ten years of age.

Fourteen cases were tested on two different days. Thirteen received different amounts of sugar on the two days, and 1 case the same amount. The fasting level in the same child varied from day to day, the average variation being 12 mg. per 100 cc. of blood, the maximum being 25 mg. per 100 cc. of blood. In 1 case the tolerance was better on one day than on another; that is, although the child

received a greater amount of sugar than on the previous day, the fasting level was reached in a shorter period of time. In 1 case where the same amount of sugar was given on two successive days the type of curve was different, although the fasting level was reached in the same period of time.

Testing the urine for sugar with Fehling's reagent in these normal children proved of little value, as this reagent is sensitive only to amounts of glucose greater than 0.1 per cent, a quantity rarely excreted by normal individuals with blood sugar below 180 mg. per 100 cc. of blood. In only 20 per cent of cases did the blood sugar rise above 180 mg. Hansen,⁵ Folin,⁶ and others, have shown in normal adults that no matter how large the amount of sugar given, the blood sugar only occasionally rises above 180 mg. per 100 cc. of blood.

In this series of cases, where the blood sugar remained below 160 mg. no positive Fehling's reaction was obtained. A positive reaction was obtained in one third of the cases, when the blood sugar ranged from 160 to 200 mg. per 100 cc. of blood. When the blood sugar was over 200 mg., a positive reaction was usually obtained in the urine. Whenever the reaction was doubtful or positive, a confirmatory yeast fermentation test was made.

Summary. 1. Eighty-four normal children from three to thirteen years of age were given varying amounts of glucose by mouth. Fourteen were tested a second time, making 98 tests in all. Blood-sugar determinations were made before the ingestion of the glucose and thereafter every half hour for two hours, including a final determination after three hours. The urine was tested with Fehling's reagent for glucose.

2. In children receiving less than 2 gm. of glucose per kilo of body weight, the blood sugar returned to the fasting level in 83 per cent of the cases at the end of three hours. When more than 2 gm. of glucose per kilo of body weight was given, 64 per cent of the cases reached the fasting level within three hours.

3. For less than 2 gm. of sugar per kilo of body weight, the tolerance is the same for children of all ages. Of children between three and six years, 96 per cent can tolerate 2 to 2.9 gm. per kilo of body weight, while only 43 per cent of the older children can tolerate this amount. The children between seven and ten years of age, appear to have a poorer tolerance for the larger amounts of glucose, than those younger than seven and older than ten.

4. The state of nutrition does not appreciably affect the sugar tolerance of children from three to six years. In children over six years of age, 77 per cent of the underweight and normal weight can tolerate less than 2.0 gm. of glucose per kilo of body weight, whereas in the overweight only 45 per cent can do so. The tolerance of all the older children for over 2 gm. per kilo of body weight is very poor, regardless of the state of nutrition.

5. Four distinct types of blood-sugar curves were obtained.
 6. The fasting blood sugar ranged from 90 mg. to 130 mg. per 100 cc. of blood; the average being 108 mg.
 7. The blood sugar in 90 per cent of the cases reached its maximum within an hour after the ingestion of the glucose. The average maximum was 180 mg. per 100 cc. of blood. In 20 per cent of the cases the blood sugar rose above 200 mg. at some time during the test.
 8. Fourteen cases were tested on two different days. The fasting level and type of curve of the same child varied from day to day. In 1 case the tolerance was better on one day than on another.
 9. Testing the urine for glucose with Fehling's solution is of little value in normal children as a test for glucose tolerance.
- Conclusions.** 1. The most satisfactory amount of glucose for testing the glucose tolerance of children from three to thirteen years of age, within a period of three hours, is 1.5 to 2 gm. per kilo of body weight.
2. Many normal children do not return to the fasting level at the end of three hours.
 3. The younger children have a better tolerance than the older for larger amounts.
 4. Children from seven to ten years of age apparently have the poorest tolerance.
 5. The state of nutrition has no effect on the tolerance of the younger children.

6. The overweight older children have a lower tolerance when the glucose is given according to body weight.

7. The fasting level, tolerance and type of curve of the same child may vary from day to day.

II. Glucose Tolerance in Relation to Nutritional Surface and Body Surface. In the foregoing, the results of glucose tolerance tests in children were described. The amount of glucose administered depended on the weight of the child. The question arose as to the accuracy of this method, as it has been long recognized that all metabolic processes bear a more constant relationship to the surface area than to the weight. The difficulty in determining the surface area has up to the present been an obstacle in using it as a basis for calculation in testing sugar tolerance.

One of the first methods used for the determination of the body surface was the Meeh-Vierordt formula, ($S.A. = 12.3 W^{\frac{2}{3}}$). This was later modified by Lissauer. Benedict and Talbot⁷ determined another constant for this formula for normal children of different weights and believe this modification to be more satisfactory. The formula used by Benedict and Talbot does not give the real body surface, but its value depends on its relationship to the two-thirds power of the weight. Another formula now in general

use is that of Du Bois which takes into consideration not only the weight but also the height of the individual. In the same category is the Pirquet nutritional surface which is calculated by squaring the sitting height. Pirquet⁸ found that the sitting height cubed is equivalent to ten times the weight.

Si = Sitting height

W = Weight.

$$Si^3 = 10 W$$

$$Si = \sqrt[3]{10 W}$$

$$Si^2 = (\sqrt[3]{10 W})^2$$

The sitting height squared, therefore, is also in relation to the two thirds power of the weight.

Using this latter formula the nutritional surface area can easily be determined by squaring the sitting height. The total calories or as Pirquet prefers to say, milk units, required per square meter of body surface can be calculated very readily. The terminology of Pirquet follows:

1 gm. milk value equals 1 nem.

0.1 gm. milk value equals 1 decinem.

1 gm. sugar is equivalent to 6 milk values or 6 nem.

0.017 gm. sugar equals 0.1 gm. milk value or 1 decinem.

In order to bring the amount of glucose into relationship to the Pirquet nutritional surface, the sitting height instead of the body weight, was used as the unit of measurement. No new tests were carried out. The grams of glucose per kilo body weight were calculated in relation to the nutritional surface and then expressed in terms of decinem.

At first 0.017 gm. of glucose or 1 decinem was given for each square centimeter of the sitting height squared, and in no case did the blood sugar return to the fasting level in three hours. Therefore, less than this was given, namely, 0.013 gm. of glucose (0.75 decinem) and 0.0085 gm. of glucose (0.5 decinem) per square centimeter of the sitting height squared. Only the results of this second group of cases were tabulated.

This calculation can be seen more readily from the following example:

A child has a sitting height of 60 cm. $Si^2 (60 \times 60) = 3600 \text{ cm.}^2$

If we wish to give 0.75 decinem for each square centimeter of sitting height squared we multiply 3600×0.75 which equals 270 nem (milk value).

Since 1 gm. of sugar is equal to 6 nem one may, by dividing 270 by 6, obtain the total grams of sugar for the test.

$$(270 \div 6 = 45 \text{ gm. of sugar})$$

If another child of the same sitting height were given 0.5 decinem, the calculation would read: $3600 \times 0.5 = 180 \text{ nem (milk value)}$; $180 \div 6 = 30 \text{ gm. of sugar}$.

Taking the amount of sugar as determined by the above calculation and dividing this amount by the weight of the child, it was found that 0.75 decinem of sugar was equivalent to 2.1 to 2.8 gm. of glucose per kilo of body weight and 0.5 decinem to 1.5 to 1.8 gm. per kilo of body weight. These comparisons should only be made in cases of normal nutrition. As previously stated it is customary to give normal adults from 1.5 to 1.8 gm. of glucose per kilo of body weight which is therefore the equivalent of 0.5 decinem in children.

TABLE IV.—TOLERANCE FOR VARYING AMOUNTS OF GLUCOSE PER SQUARE CENTIMETER OF SITTING HEIGHT SQUARED.

Glucose per sq. cm. sitting height squared.		End of 2 hours.			End of 3 hours.		
Decinem.	Grams.	Total cases.	Returned to fasting level.		Total cases.	Returned to fasting level.	
			Cases.	Per cent.		Cases.	Per cent.
0.5	0.0085	53	21	40	53	44	83
0.75	0.0130	38	13	34	33	22	66

The glucose tolerance of all children regardless of age for 0.75 decinem and 0.5 decinem of glucose has been tabulated in Table IV.* When 0.75 decinem was given, the blood sugar of only 34 per cent of the cases returned to the fasting level at the end of two hours, and 32 per cent more returned to the normal at the end of three hours, a total of 66 per cent returning to the fasting level at the end of three hours. When 0.5 decinem was given, 40 per cent of the cases returned to the fasting level at the end of two hours, and 44 per cent more at the end of three hours, a total of 83 per cent returning to the fasting level at the end of three hours. This fact was noted in the first part of the paper, namely, that only 83 per cent of children can tolerate less than 2 gm. of glucose per kilo of body weight which is the equivalent of 0.5 decinem in the normal state of nutrition.

The glucose tolerance in relation to the age of the children can be seen from Table V. When 0.5 decinem is given the tolerance is the same for all ages. When 0.75 decinem is given the tolerance of older children is not as good as that of the younger children. The children between seven and ten years receiving 0.75 decinem have a poorer tolerance than those older than ten and younger than seven.

* For practical purposes those cases whose blood sugar returned within 15 mgr. of the fasting level, were included in the total percentage.

TABLE V.—TOLERANCE IN RELATION TO AGE AND AMOUNT OF GLUCOSE PER SQUARE CENTIMETER OF SITTING HEIGHT SQUARED.

Age, yrs.	Glucose per sq. cm. sitting height squared.		End of 2 hours.			End of 3 hours.		
	Decimem.	Grams.	Total cases.	Returned to fasting level.		Total cases.	Returned to fasting level.	
				Cases.	Per cent.		Cases.	Per cent.
3 to 6 . . {	0.50	0.0085	24	9	36	24	20	83
	0.75	0.0130	17	6	35	16	14	86
7 to 9 . . {	0.50	0.0085	12	2	17	12	10	84
	0.75	0.0130	10	0	0	8	2	25
10 to 13 . . {	0.50	0.0085	17	9	53	17	15	88
	0.75	0.0130	11	3	27	9	5	56

To determine whether the carbohydrate tolerance is affected by the state of nutrition, the children were grouped into 3 classes according to the Pirquet standard.* The relation of the glucose tolerance to the state of nutrition can be seen from Table VI.

- I. Underweight: Pirquet index less than 93.
- II. Normal weight: Pirquet index of from 93 to 97.
- III. Overweight: Pirquet index more than 97.

Pirquet uses the formula $100 \frac{\sqrt[3]{10 W}}{Si}$ as a nutrition index. Tables have been compiled giving the Pirquet index for varying weights and sitting heights. Austrian school children of a normal state of nutrition have an index of between 93 to 97.

It was of interest to compare this system with that of the Baldwin-Wood Height, Weight, Age Index. None of these nutritional systems are infallible as has been shown by Clark, Sydenstricker and Collins,⁹ Baker and Blumenthal,¹⁰ and Dublin and Gebhart.¹¹ These authors have shown that occasionally a child considered underweight by one standard is normal or in rare instances overweight by another. Not infrequently a physician's clinical diagnosis of the state of nutrition does not agree with the mathematical standard. According to the Pirquet standard 33 per cent of the children tested

* Basis for calculation of Pirquet nutrition standard:

$$\begin{aligned}
 Si &= \text{Sitting height} \\
 10 W &= \text{Ten times the weight} \\
 Si^2 &= 10 W \\
 Si &= \sqrt[3]{10 W} \\
 \frac{\sqrt[3]{10 W}}{Si} &= 1
 \end{aligned}$$

were underweight and 21 per cent, overweight. If the Pirquet index of 92 had been taken as the lower limit of normal nutrition instead of 93, then 23 per cent of the cases would have been classed as underweight, which was the same percentage obtained when these children were grouped according to the Baldwin-Wood standard.

TABLE VI.—TOLERANCE PER SQUARE CENTIMETER SI^2 IN RELATION TO AGE, AMOUNT OF GLUCOSE, AND STATE OF NUTRITION.

Age, yrs.	Glucose per sq. cm. sit- ting height squared		Pirquet nutri- tional index.	End of 2 hours.			End of 3 hours.		
	Decinem.	Grams.		Total cases.	Returned to fasting level.		Total cases.	Returned to fasting level.	
					Cases.	Per cent.		Cases.	Per cent.
3 to 6	0.50	0.0085	-93	7	3	44	7	4	66
			93 to 97	13	9	70	13	12	92
			98+	4	0	0	4	4	100
	0.75	0.0130	-93	3	1	33	3	3	100
			93 to 97	10	4	40	9	9	100
			98+	4	1	25	4	3	75
7 to 13	0.50	0.0085	-93	13	5	38	13	11	84
			93 to 97	12	5	42	12	11	92
			98+	4	2	50	4	2	50
	0.75	0.0130	-93	5	1	20	5	3	60
			93 to 97	8	0	0	7	2	29
			98+	8	2	5	5	3	60

When taking into consideration the age of the child concomitantly with the Pirquet nutrition index as shown in Table VI, there is practically no difference in the tolerance for 0.5 decinem in younger and older children, regardless of their state of nutrition. When 0.75 decinem is given to the younger children the blood sugar of the underweight and normal ones returns to the fasting level within the time limits of the test. There are too few young obese individuals to make any definite statement. In the older children 0.75 decinem is apparently too much, regardless of the state of nutrition. From Table VI the normal older children receiving 0.75 decinem appear to have a lower tolerance, but this fact is a result of the chance inclusion of the children between seven and ten years of age who were previously shown to have a poorer tolerance.

As noted in Part I, when the amount of glucose given was in relation to the body weight, the older overweight children had a lowered sugar tolerance. But this was not true when the amount of glucose administered was in relation to Pirquet nutritional surface. When this latter method was used the tolerance of under-

weight, normal—and overweight children was approximately the same. This is readily understood when it is considered that the sitting height, which is used as the basis of calculation, is a linear measurement and is the third root of the expected weight and not of the actual weight. Therefore, the amounts given are independent of the state of nutrition, which is not the case when the amount of glucose is based on the body weight. This fact is brought out clearly in Table VII where 0.5 decinem is expressed in terms of grams per kilo for the two age groups of different states of nutrition. The younger and more underweight a child is, the larger is the amount given in terms of grams per kilo of body weight; the older and heavier, the less glucose does it receive per kilo of body weight.

TABLE VII.—EFFECT OF AGE AND NUTRITIONAL CONDITION OF CHILDREN ON GLUCOSE DOSAGE USING PIRQUET SYSTEM.

Age, yrs.	Pirquet index.	Glucose per sq. cm. sitting height squared.		Average grams per kilo body weight.
		Decinem.	Grams.	
3 to 6 . . .	93	0.5	0.0085	1.85
	93 to 97	1.66
	98+	1.60
7 to 13 . . .	—93	0.5	0.0085	1.58
	93 to 97	1.50
	98+	1.20

Comparing two children of the same sitting height, a heavy child may receive as much as 0.5 gm. less per kilo than a thin child. Therefore, calculating the amount of glucose for a tolerance test the amount of surface area instead of weight is more satisfactory.

Table VIII gives the details of all the examinations upon which this article is based.

Summary. 1. In Part I of this paper, the amount of glucose administered was calculated from the body weight of the child; in Part II, the amount of glucose was calculated in relation to the nutritional surface of the child. The Pirquet nutritional surface was used, the sitting height being the unit of measurement. The amounts of glucose given are expressed in terms of decinem.

2. In those cases receiving 0.5 decinem of glucose, in 83 per cent of the cases the blood sugar returned to the fasting level at the end of three hours, and in those receiving 0.75 decinem 66 per cent of cases returned to the fasting level in three hours.

3. The tolerance of children of all ages is the same for 0.5 decinem of glucose. When given 0.75 decinem, 86 per cent of the children between three and six years, 25 per cent of the children from seven to nine years, and 56 per cent of the children from ten to thirteen years returned to the fasting level in three hours.

Case No.	Age.	Sex.	Weight, kilo.	Length, cm.	Sitting height, cm.	Body surface, (DuBois-Linear), sq. m.	Nutritional index.		Glucose.			Blood-sugar percentage.					
							Variation from Wood.	Pirquet.	Grams per kilo body weight.	Decimem per Sq. Cm ² per Sq.	Grams per sq. m. body surface.	Fasting.	30 minutes.	60 minutes.	90 minutes.	120 minutes.	180 minutes.
{ 88. * 86. 70	3	M.	16.0	98	57	0.64	0	96	1.50	0.50	42	0.115	0.160	0.150	0.120	0.105	0.110
	3	M.	16.0	98	57	0.64	0	96	2.00	0.65	50	0.100	0.200	0.170	0.180	0.160	0.100
	77	M.	14.5	92	56	..	0	94	1.70	0.50	..	0.105	0.170	0.177	0.112	0.125	0.108
32	3	M.	13.5	88	52	..	+ 2	98	2.00	0.50	..	0.130	0.210	0.180	0.250	0.150	0.100
43	3	F.	16.7	102	59	0.70	+ 1	95	2.50	0.75	61	0.090	0.190	0.170	0.120	0.090	0.090
33	3	M.	16.0	96	56	0.65	+ 4	95	2.55	0.75	65	0.108	0.200	0.160	0.130	0.105	0.120
31	3	F.	13.0	88	52	..	+ 2	98	2.60	0.75	..	0.095	0.200	..	0.160	0.105	0.105
{ 63. * 58. 91	4	M.	18.6	110	63	0.77	0	91	1.50	0.40	35	0.130	0.220	0.240	0.244	0.250	0.190
	4	M.	18.6	110	63	0.77	0	91	1.80	0.50	43	0.085	0.110	0.180	0.220	0.160	0.190
	91	M.	18.2	98	57	0.69	+16	99	1.50	0.50	39	0.107	0.164	0.160	0.185	0.140	0.100
39	4	M.	26.0	100	58	0.78	+35	110	1.60	0.75	54	0.095	0.200	0.220	0.200	0.145	0.145
{ 33. * 30. 92	4	F.	14.0	90	53	..	- 1	98	1.70	0.50	..	0.095	0.190	0.175	0.130	0.120	0.095
	4	F.	14.0	90	53	..	- 1	98	2.50	0.75	..	0.100	0.150	..	0.250	0.170	0.120
	92	M.	15.5	98	57	0.65	- 2	94	1.70	0.50	41½	0.110	0.180	0.180	0.180	0.140	0.105
72	4	M.	15.5	92	54	0.60	+15	100	2.00	0.65	50	0.120	0.190	0.176	0.180	0.220	0.130
76	4	M.	15.2	94	55	0.60	0	97	2.00	0.60	50	0.125	0.180	0.140	0.150	0.125	0.125
23	4	M.	17.1	94	55	0.60	+11	101	2.30	0.75	65	0.110	0.140	0.170	0.150	0.160	0.135
20	4	M.	15.4	92	54	0.60	+15	100	2.40	0.75	59	0.115	0.120	0.150	0.170	0.190	0.102
99	4	M.	18.0	104	60	0.70	+ 1	95	2.50	0.75	65	0.110	..	0.160	0.184	0.170	0.110
42	4	F.	16.0	98	57	0.65	- 1	96	2.50	0.75	63	0.120	0.180	0.130	..	0.140	0.110
18	4	M.	15.9	105	60	0.68	-12	91	2.80	0.75	66	0.117	0.200	0.186	0.150	0.200	0.120
11	4	M.	15.4	102	58	0.67	0	93	2.90	0.75	59	0.105	0.160	0.164	0.174	0.160	..
56	5	F.	16.8	97	57	0.67	+ 8	97	1.60	0.50	41	0.100	0.130	0.140	0.120	0.100	0.100
74	5	M.	19.1	92	63	0.73	0	92	1.60	0.50	43	0.125	0.190	0.148	0.170	0.150	0.160
{ 73. * 75. 54	5	M.	20.4	108	62	0.77	+ 8	95	1.70	0.50	47	0.110	0.190	0.170	0.170	0.125	0.125
	5	M.	20.4	109	62	0.76	+ 8	95	2.00	0.60	52	0.120	0.190	0.170	0.184	0.154	0.600
	5	F.	17.5	106	60	0.72	+ 6	94	2.00	0.60	50	0.120	0.190	0.200	0.135	0.130	0.100
{ 50. * 50. 53	5	F.	17.5	106	60	0.72	+ 6	94	2.00	0.60	50	0.080	0.152	0.160	0.180	0.130	0.100
	5	F.	17.5	106	60	0.72	+ 6	94	2.00	0.60	50	0.080	0.152	0.160	0.180	0.130	0.100
	5	M.	18.6	108	61	0.74	- 2	94	2.00	0.60	50	0.115	0.185	0.130	0.140	0.125	0.135
* 57	5	M.	18.2	108	61	0.74	- 3	94	1.70	0.50	43	0.096	0.200	0.150	0.150	0.108	0.090

29	M.	18.6	108	61	0.74	-4	94	2.20	0.70	57	0.095	0.175	0.160	0.180	0.160	0.120
14	M.	18.6	102	59	0.70	+6	97	2.30	0.75	62	0.125	0.240	0.180	0.178	0.170	0.125
35	M.	15.7	100	57	0.65	-2	95	2.60	0.75	63	0.100	0.190	0.150	0.170	0.170	0.110
6	F.	18.0	110	62	0.74	-10	92	1.50	0.40	36	0.120	0.180	0.170	0.140	0.130	0.090
6	F.	17.7	110	62	0.74	-11	91	1.80	0.50	43	0.115	0.135	0.180	0.190	0.140	0.105
6	F.	20.4	112	62	0.80	-1	95	1.60	0.50	38	0.103	0.140	0.135	0.120	0.170	0.122
59	M.	16.4	108	61	0.70	-14	90	1.90	0.50	44	0.110	0.180	0.180	0.160	0.105	0.090
28	F.	16.3	109	61	0.70	-20	89	2.50	0.65	60	0.110	0.220	0.180	0.160	0.128	0.110
100	M.	18.0	120	67	0.85	-11	89	2.60	0.75	65	0.100	0.160	0.156	0.110	0.100	0.100
102	F.	21.0	106	61	0.75	0	93	2.60	0.75	60	0.110	0.170	0.160	0.135	0.120	0.125
93	M.	17.5	106	60	0.70	-12	90	2.90	0.75	102	0.100	0.160	0.180	0.156	0.154	0.120
2	M.	21.4	122	66	0.85	-17	88	4.40	1.00	51	0.125	0.220	0.231	0.210	0.220	
61	F.	20.0	108	61	0.75	+6	96	1.60	0.50	43	0.106	0.130	0.195	0.190	0.145	0.105
27	M.	21.3	114	65	0.80	+2	93	1.65	0.50	44	0.110	0.150	0.230	0.190	0.190	0.120
96	F.	32.3	128	71	1.05	+16	97	1.95	0.75	60	0.130	0.175	0.180	0.200	0.184	0.130
51	F.	20.9	116	65	0.82	-10	92	2.00	0.60	51	0.115	0.230	0.165	0.175	0.165	0.115
7	M.	25.6	120	66	0.90	+6	97	2.10	0.75	60	0.118	0.230	0.230	0.198	0.180	
8	F.	21.3	120	66	0.83	-10	91	2.10	0.75	56	0.115	0.200	0.200	0.200	0.170	
104	M.	19.4	112	63	0.88	-7	91	2.50	0.75	67	0.092	0.164	0.170	0.110	0.200	0.130
106	M.	33.0	128	70	1.06	+18	98	1.25	0.50	39	0.120	0.230	0.200	0.160	0.125	0.102
89	M.	32.3	130	71	1.05	+9	97	1.30	0.50	40	0.110	0.240	0.220	0.160	0.200	0.160
22	F.	23.6	122	67	0.90	-2	93	1.66	0.50	43	0.110	0.200	0.142	0.160	0.170	0.125
8	F.	12.7	106	60	0.75	-5	94	1.80	0.50	40	0.090	0.180	0.160	0.160	0.150	0.115
55	M.	22.0	120	66	0.85	-10	92	1.90	0.60	51	0.130	0.185	0.200	0.180	0.155	0.100
101	M.	26.4	120	67	0.92	+6	96	2.20	0.75	64	0.110	0.250	0.250	0.220	0.160	0.160
13	M.	23.2	122	67	0.89	-7	92	2.50	0.75	62	0.125	0.190	0.190	0.220	0.180	0.180
94	F.	17.3	104	58	0.70	-4	95	2.50	0.75	61	0.125	0.170	0.194	0.192	0.156	0.156
1	F.	21.8	120	66	0.85	-8	91	3.30	1.00	86	0.125	0.250	0.210	0.210	0.210	
36	M.	50.0	144	77	1.44	+27	103	1.50	0.75	52	0.105	0.240	0.240	0.200	0.200	0.160
37	M.	50.0	144	77	1.44	+27	103	1.10	0.50	31	0.130	0.250	0.140	0.200	0.135	0.100
26	M.	30.0	134	73	1.05	-1	92	1.50	0.50	42	0.098	0.184	0.260	0.200	0.190	0.130
41	M.	26.0	130	71	1.00	-11	90	1.60	0.50	42	0.115	0.145	0.178	0.160	0.160	0.105
105	M.	31.4	130	70	1.05	+9	98	1.90	0.75	57	0.095	0.100	0.130	0.140	0.150	0.110
95	F.	23.6	120	66	0.90	0	94	2.30	0.75	60	0.100	0.170	0.160	0.180	0.180	0.160
40	M.	28.8	130	70	1.10	-2	94	1.40	0.50	37	0.126	0.200	0.180	0.115	0.120	0.100
52	F.	27.7	128	70	1.00	-5	93	1.50	0.50	41	0.130	0.180	0.140	0.155	0.130	0.100
82	F.	28.6	134	72	1.03	-4	92	1.50	0.50	42	0.130	0.180	0.224	0.220	0.125	0.085
83	M.	28.0	134	73	1.04	-14	90	1.55	0.50	40	0.095	0.200	0.155	0.180	0.170	0.105
5	M.	29.0	128	69	1.08	+6	98	2.00	0.75	54	0.125	0.216	0.155	0.122	0.136	
107	M.	44.0	144	77	1.30	+24	103	1.80	0.75	56	0.110	0.162	0.160	0.156	0.160	0.160
108	M.	44.0	144	77	1.30	+24	103	1.10	0.50	35	0.106	0.130	0.160	0.140	0.142	0.140

* Cases in brackets represent the same child tested on two different days.

TABLE VIII.---(Continued.)

Case No.	Age.	Sex.	Weight, kilo.	Length, cm.	Sitting height, cm.	Body surface, (DuBois-Linear), sq. m.	Nutritional index.		Glucose.			Blood-sugar percentage.					
							Variation from Wood.	Pirquet.	Grams per kilo body weight.	Decimem per Cm ² per Sq.	Grams per sq. m. body surface.	Fasting.	30 minutes.	60 minutes.	90 minutes.	120 minutes.	180 minutes.
90	10	M.	24.4	124	67	0.91	- 5	94	2.00	0.75	55	0.120	0.188	0.150	0.134	0.164	0.124
17	10	M.	24.2	122	66	0.91	+ 1	95	2.20	0.75	59	0.130	0.184	0.160	0.190	0.180	0.170
97	10	M.	22.7	122	67	0.89	- 9	91	2.35	0.75	62	0.120	0.246	0.290	0.220	0.200	0.164
3	10	F.	30.0	136	73.5	1.07	- 7	92	3.00	1.00	83	0.112	0.240	0.240	0.240	0.180	
{84	11	M.	30.0	138	74	1.08	- 9	91	1.50	0.50	42	0.105	0.175	0.140	0.130	0.165	0.110
*{87	11	M.	30.0	138	74	1.08	- 19	91	1.80	0.60	50	0.110	0.170	0.194	0.170	0.148	0.096
{80	11	F.	27.3	122	71	0.95	+ 10	92	1.50	0.50	44	0.090	0.130	0.135	0.120	0.108	0.108
*{81	11	F.	27.2	122	71	0.95	+ 10	92	1.80	0.60	50	0.103	0.115	0.160	0.170	0.124	0.120
10	11	F.	45.0	144	78	1.32	+ 14	99	1.60	0.75	58	0.127	0.170	0.220	0.204	0.186	
85	11	M.	28.0	122	71	0.95	+ 10	93	1.70	0.60	50	0.110	0.180	0.180	0.180	0.115	0.110
98	11	M.	38.0	138	74	1.20	+ 11	98	1.80	0.75	57	0.120	0.210	0.210	0.180	0.180	0.140
6	11	M.	29.0	124	69	0.93	+ 10	98	2.00	0.75	59	0.125	0.240	0.240	0.190	0.155	
15	11	F.	19.5	112	61	0.87	- 8	95	2.40	0.75	54	0.120	0.190	0.200	0.210	0.190	0.145
16	11	F.	24.5	120	70	0.95	- 19	90	2.50	0.75	64	0.125	0.168	0.115	0.124	0.120	0.110
{46	12	M.	35.2	136	73	1.17	+ 9	97	0.80	0.33	25	0.120	0.110	..	0.125	0.130	0.110
*{48	12	M.	36.0	136	73	1.17	+ 9	97	1.20	0.50	38	0.120	0.110	0.130	0.160	0.115	0.110
62	12	F.	47.3	146	78	1.39	+ 15	100	1.10	0.50	37	0.110	0.190	0.160	0.160	0.150	0.135
{45	12	M.	41.0	144	77	1.27	+ 7	97	0.90	0.33	26	0.112	0.240	..	0.120	0.120	0.120
*{49	12	M.	41.0	144	77	1.27	+ 7	97	1.20	0.50	38	0.110	0.130	0.155	0.150	0.140	0.090
65	12	M.	37.3	140	75	1.20	+ 5	96	1.25	0.50	39	0.120	0.200	0.140	0.130	0.120	0.125
78	12	M.	30.0	128	74	1.05	0	91	1.50	0.50	42	0.098	0.168	0.150	0.155	0.140	0.102
103	12	M.	30.0	128	69	1.05	+ 1	99	2.00	0.75	56	0.100	0.210	0.190	0.110	0.110	0.100
4	12	M.	35.0	142	76	1.18	- 4	92	2.70	1.00	82	0.130	0.194	0.190	0.180	0.190	
{34	13	M.	21.0	128	69	0.50	- 25	86	1.80	0.50	44	0.120	0.175	0.160	0.184	0.184	0.128
*{44	13	M.	22.3	128	69	0.90	- 20	89	1.20	0.33	29	0.110	0.120	..	0.135	0.105	0.095
25	13	M.	28.6	122	71	0.98	+ 10	93	1.50	0.50	44	0.130	0.184	0.210	0.180	0.200	0.120

* Cases in brackets represent the same child tested on two different days.

4. In using the sitting height squared as the unit for calculation, the state of nutrition plays no role and therefore can be disregarded.

Conclusions. 1. When using the Pirquet nutritional surface for calculating the amount of glucose to be administered, 0.5 decinem of glucose is the most satisfactory amount to give to children aged three to thirteen years.

2. Children of all ages have the same tolerance for 0.5 decinem of glucose per square centimeter of sitting height squared.

3. The younger children have a better tolerance than the older ones when more than 0.5 decinem is given.

4. Since in a child of normal weight 0.5 decinem is equivalent to 1.5 to 1.8 gm. of glucose per kilo of body weight, it is immaterial whether the glucose is calculated from the body weight or the nutritional surface.

5. It is more accurate to calculate the amount of glucose from the nutritional surface than body weight in the overweight and underweight children.

6. Since the Pirquet formula $Si^2 = (\sqrt[3]{10 W})^2$ has the similar two-thirds power relation to the weight as the Meeh-Vierordt and Lissauer formulæ, there is no doubt that these latter formulæ could also be used for calculation. Their use however is more difficult, as the calculation of the Pirquet formula needs only the simple squaring of the sitting height, whereas the other formulæ necessitate the use of logarithmic tables.

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COMMENTS ON BODY WEIGHT IN RELATION TO HEALTH AND DISEASE.*

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Introduction. I have selected for my address the subject of body weight in relation to health and disease. I realize the breadth of this theme, and will, therefore, confine my remarks to certain significant phases of the subject as they bear on the problem of clinical medicine.

The measurement of body weight and its practical importance is an evolution in the scientific study of nutrition, which dates to the sixteenth century, when that great investigator, Lavoisier,¹ applied the quantitative method to the study of chemistry. The marked strides of the past two decades, made in the field of the metabolic disease, are founded on the investigations of the nineteenth century continental observers, starting with François Magendie, followed by Liebig, Voit, and Rubner, and carried forward in our own country by that able band of scientists, dominated particularly by the researches of Lusk, Benedict, Du Bois and McCollum.

Preliminary Physiological Considerations. Before discussing in detail the unusual deviations from the normal body weight, I should like to direct attention to some of the fundamental physiological mechanisms which control weight variation, as observed in the human organism. We all recognize that individuals normally have a tendency to maintain a certain average body weight. The essential factor in the maintenance of this constant level is brought about by the regular intake of water and food. Variation in the water content of the body is a well-known cause of alteration in weight, and is particularly noted after strenuous exercise, or it may be associated with disease, in which the water balance is disturbed. This is commonly seen in nephritis and diabetes.

The body energy is supplied primarily by food. The potential energy of the food absorbed is liberated in the metabolism and leaves the organism as heat. If the amount of energy available to the body in the food absorbed is greater than the amount lost from the body, the excess is stored in the tissues in the form of combustible materials, as proteins, carbohydrates, and fat. The capacity of the body to store protein and carbohydrate is limited, however, so that any considerable storage of excess energy is accomplished by a deposit of fat. On the other hand, if the energy liberated during the metabolism exceeds that which is available in the food absorbed, the deficiency is supplied by a combustion of the

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energy-containing material stored in the body. Eventually, this means a consumption of fat.

The body also possesses a mechanism that operates to prevent wide fluctuations in weight, which might follow changes in the habits of the individual. This adjustment lies in the alteration in the rate of combustion to conform to the food intake, and also by an alteration in the food intake, to meet the energy needs of the organism. Following the intake of food there is a temporary rise in the combustion. This effect is more marked after the consumption of protein, though to a less extent after carbohydrate and fat. The marked rise in the combustion following high protein intake is an interesting phenomenon, first noted experimentally in 1852 by Bidder and Schmidt, (McCollum²) and later studied more carefully by Rubner, who termed it the specific dynamic action of protein. Recent studies of Lusk, (1915³) indicate that the specific dynamic action of protein is caused by a stimulative effect of specific amino-acids on the oxidative processes of the organism.⁴

In summary then, we may say, with regard to the chief physiological mechanism controlling body weight, that in the normal individual the weight appears to be maintained primarily through an adjustment of food intake to the body needs. The adjustment of the rate of metabolism to correspond with food intake probably becomes an important factor only under unusual conditions.

Standards of Normal or Ideal Weight. Various formulæ have been devised for the estimation of normal weight of persons of different height, sex, and age. In practice it cannot be said that any of these standards have been entirely satisfactory when applied to unselected clinical cases. This handicap of uncertainty, with regard to normal or ideal weight, has been very obvious to those who have dealt with metabolic disease, where it is often necessary to estimate an ideal weight for a given individual.

The difficulty has arisen because of the great number of variable factors which must be taken into consideration, when such a standard is applied. A truly comprehensive formula must take into consideration the following factors: age, height, sex and body build. The numerous insurance tables, based on determinations made on applicants for life insurance, are derived from age, height, and sex; body build is entirely ignored.

In my experience, perhaps the most comprehensive prediction tables available for the estimation of normal weight, are those devised by Dreyer⁵ in England during the World War. In his attempt to work out a method for the assessment of physical fitness, he formulated tables from which the normal or ideal weight can be ascertained by using the physical measurements of weight, length of trunk, and chest circumference. With this method the important factor of body build is given its relative significance; whereas age is disregarded, except that the tables apply only to adults. Dreyer's

method, on the whole, probably represents the most scientific and adequate formula for predicting normal weight we have at our disposal.

Overweight and Obesity. Proceeding now to the discussion of the pathological states of body weight and their relation to disease, I will first direct attention to the condition of overweight or obesity.

Overnutrition is extremely prevalent in America and obesity is one of our most common diseases. Du Bois⁶ has recently said: "The large amount of public opinion on this subject is in marked contrast to the small amount of scientific information we have regarding it." This statement is particularly true with regard to our knowledge of the exact biochemical and physiological abnormalities, which all agree, must in the final analysis underlie the problem of obesity. Nevertheless, observations are accumulating, some clinical and some chemical, bearing on this subject.

Obesity has usually been divided into two groups, the simple or exogenous type, presumably due to excessive intake of food combined with too little exercise, and the endogenous type, in which those affected frequently possess a lowered combustive power, associated with a disturbance in the endocrine domain.

Recent investigations by Strouse^{7,8,9} and his coworkers on the metabolism of obesity, suggest that there is probably a third type, which he tentatively designates a true constitutional variety. This group is characterized by an inability to lose weight on very low total caloric diets of 600 to 1000 calories a day, even though this intake is maintained over a prolonged period; the basal metabolic rate is found to be consistently within normal limits, but there is a definite tendency to a lowering of the specific dynamic action of protein. This type of individual, therefore, appears to possess a metabolism functioning with an unusual economy and represents a true metabolic anomaly, not associated with an endocrine disturbance or excessive food intake. In other words, it can be differentiated by the foregoing criteria from the exogenous and endogenous groups of the older observers.

To return now for a moment to these last mentioned varieties, the exogenous and the endogenous, I will dismiss them with a few words.

The exogenous is probably the most common type of obesity. In this condition, proper management by the physician with coöperation on the part of the patient, afford striking therapeutic results. The basal metabolic rate in these patients is always within normal limits.¹⁰

In the endogenous group proper, a frank endocrine etiology is usually apparent. I cannot, however, agree that obesity of this type is particularly frequent in adults, when compared with the great number of cases seen in the other two groups. The cases of adiposity I have studied that can be properly included as strictly endogenous

in origin, can be grouped clinically into three classes, depending upon which ductless gland is involved predominately:

1. The thyrogenous class, concerning which all agree, presents the well known picture of myxedema and is found to have a lowered metabolic rate. The adiposity of myxedema is less constant and striking than the undernutrition seen in hyperthyroidism.

2. The gonad class, which occurs practically only in the postadult age.¹¹ The justification for distinguishing this variety of adiposity rests on considerable experimental evidence as noted in the effects of castration in animals and man.

3. The hypophyseal class, though striking clinically, in the picture of Fröhlich's syndrome and its modifications, rests on a less secure scientific basis as to its exact nature. The recent work of Smith¹² and Evans¹³ on the anterior lobe of the pituitary and that of Abel¹⁴ on the posterior lobe, have added important facts regarding the complex function of this gland, and give promise of finally establishing clinical entities on a real physiological basis.

Speaking generally, it is the endogenous group of adiposities where alterations in the normal metabolic rate can be sought with most optimism, and likewise, in which, organotherapy offers most from the therapeutic standpoint.

With this sketch of our present-day conceptions of the types of obesity, I will pass to a brief consideration of certain diseases which appear to have some relation to the condition of overweight, opening this discussion with diabetes mellitus.

Overweight and Diabetes. The association of overweight and diabetes has long been noted, while in the presence of a wasting disease diabetes is practically unknown. Perhaps we owe more to Joslin and Allen than to other students of this disease, for the stress they have put upon obesity as a frequent prediabetic condition. Joslin¹⁵ states that in 1063 cases of diabetes marked obesity preceded the onset of this disease in more than 40 per cent. The intimate relationship of excess body weight to diabetes is clearly emphasized by the following well known observations.

Reduction in weight in diabetes is associated with marked benefit, as evidenced by a clearing up of the active symptoms, and a gain in the assimilative power. We believe this is related to an increase in the effective mass of active pancreatic islets relative to the size of the individual. On the other hand, a gain in weight is frequently followed by a reduction of the sugar tolerance.

A word at this point about the gain of weight following the use of insulin may not be amiss. The most spectacular increase in weight following insulin occurs in patients suffering marked emaciation, acidosis and dehydration. This prompt increase of weight is associated with changes in the fluid balance, as can be shown by recording the fluid intake and output. It is found that the increase of weight is largely due to fluid retention. The type of diet served

the severe diabetic is rich in mineral salts, and these assist in maintaining a normal osmotic pressure in the tissues so that the patient quickly attains a plump appearance, while the tissue turgor is distinctly increased. The amount of weight increase in emaciated patients due to stored fluid without edemâ may be astonishing.

Body weight affords a valuable index of the clinical state in this disease, and the diabetic who is maintained at a body weight between normal and 15 per cent below normal, I feel, is in the most satisfactory condition.

All obese patients should be studied with reference to their sugar tolerance as determined by a blood-sugar curve, and a quantitative measurement of urinary sugar and fluid output. I am convinced that further observations of this character will aid in clearing up some of the uncertainties now surrounding the relationship of obesity to diabetes, and further, it will enable us to discover individuals whose lowered sugar tolerance augurs the onset of this disease.

Surgical Aspects of the Obese. I should like to make a plea for the close coöperation of the surgeon and the internist in the management of the obese patient on whom prospective surgery is anticipated. Until recently, patients handicapped thus were regarded as potentially grave surgical risks, and so accepted by the surgeon without due consideration of the possibilities of preoperative preparation and postoperative management.

The obese patient has been recognized as a grave surgical risk for years, not only because of the mechanical difficulty of the operation, but because he is prone to unfortunate complications such as infection, the tardy healing of wounds, and fat embolism.

The preoperative care of the obese will reduce the operative mortality by half. This preparation should aim to reduce the body weight by 10 to 20 per cent by a restriction in the total diet, and especially curtailing the fat and carbohydrate components. A rest period in bed for a week or ten days is also of decided value in obtaining better relaxation of the abdominal musculature.

Ether is probably the anesthetic of choice. Local anesthesia is less satisfactory in the obese than in the ordinary subject, because the infiltration of fatty tissues tends to produce necrosis and retards healing. It must be remembered that the reparative process of tissues is slower in these individuals at best. Surgeons have recognized the peculiarities of healing in the obese and have, therefore, learned that they should be especially careful in handling fatty tissue to prevent trauma, and to reduce manipulation to a minimum. In closing the incision, dead spaces should be particularly avoided.

The postoperative management should aim to prevent pulmonary complications, cardiac failure, wound infection, reopening of the wound, hernia, and fat embolism. Healing should be complete before the patient is allowed up.

Team work between the surgeon and the internist is the keynote to successful surgery in the obese.

Cardiovascular Diseases Including Arterial Hypertension and their Relation to Overweight. I wish to discuss next the association of cardiovascular diseases including arterial hypertension and overweight.

There are three definite conditions, which though in no way part of the general process of obesity, are frequently associated with it, namely coronary sclerosis, hypertension and atrophy of the heart muscle. Needless to say these conditions may occur singly or combined, and are increased in their clinical significance by the presence of a high diaphragm which is a common finding in the obese type of body build.

In the present state of our knowledge, perhaps the most important bearing of obesity to circulatory disease depends upon the general mechanical burden enforced on the cardiovascular system. In younger individuals, without a history of heart damage following infection, and in whom the overweight has been of comparatively recent origin, this handicap is not so apparent; whereas, in the older patients, and particularly those of long-standing obesity, the circulatory complications are of great significance, both in the incapacitating effects and in endangering the prognosis.

I do not wish to dwell at length on the important bearing of overweight to the degenerative cardiovascular diseases, but I should like to add just a word concerning this condition and arterial hypertension.

At the present time we have no scientific proof of an etiological connection between obesity and hypertension, despite the common clinical experience, that reduction in weight is at times followed by a reduction in the systolic blood pressure and marked improvement in subjective symptoms.

Orthopedic Problems and Obesity. I am convinced that any one who sees a number of obese patients will be struck by the prominence of certain orthopedic problems associated with the state of well marked overweight. At least this has been my own experience in the Metabolic Clinic of the Out-patient Department of the University of California Hospital during the past four years. In general it appears to me that these problems are of two kinds however the two groups are not always entirely separable.¹⁶ The first pertains to the association of arthritis in the obese, whereas the second deals more specifically with certain postural and static difficulties, combined with faulty bodily mechanics, seen in these patients.

To consider first the arthritis of the obese, I wish to make it clear from the outset that I am not one of those who believe with Pemberton that arthritis is primarily a metabolic disorder. In my opinion, the weight of evidence at the present time indicates that

arthritis is a problem of physiology and biochemistry, in which infection probably plays the essential, precipitating role. My theme in regard to the association of arthritis and obesity is somewhat as follows: The sedentary habits of the obese predispose to muscular atrophy both in the skeletal and cardiac musculature. This rarely appears before the thirty-fifth year of life. It is not a long stretch of the imagination to assume that joint changes also occur in these individuals, as a comparable degenerative process. With the presence of points of low resistance and possibly disturbed circulation in structures of such anatomy and function as the joints, the soil is prepared for the ready production of local changes of cartilage at the joint margins. Foci of infection can usually be demonstrated in these cases and are probably the precipitating and essential factor in the process, although this point remains unsettled. The arthritis of the obese is usually the hypertrophic or degenerative variety and causes disability from the mechanical irritation of the bony spurs, rather than from an active inflammatory process in the ordinary sense.

From the clinical standpoint, one of the most important groups of cases, is represented by the low back pain of hypertrophic arthritis. This is usually due to strain of a spine in which there is already limitation of motion, and is sometimes precipitated by external trauma. The therapeutic indications in this group comprise improvement of the body mechanics combined with protection of the back by suitable support from further strain and an attempt to arrest the arthritis.

The postural and static difficulties of the obese are common and well recognized and result primarily from faulty bodily mechanics. There is a basic principle, accepted and utilized by the orthopedists, but not so fully appreciated and applied by the internists,¹⁷ that the use of the body in faulty mechanical alignment is always a potential source of trouble. Goldthwait,¹⁸ in the Shattuck Lecture, in 1915, drew attention to the types of body build and their significance in medical disease. The group of individuals prone to develop postural disturbances and hypertrophic arthritis are represented in the so called herbivorous class. The abnormally large and heavy abdominal viscera in these people leads to backward inclination of the body, which produces a strain at the dorsolumbar juncture. The strain thus produced upon the lower back leads to a sensitiveness at the lumbosacral juncture, and in this way, accounts for some cases of lumbago. Another common form of spinal deformity closely allied with the condition just mentioned is scoliosis. The pelvis is apt to be thrown backward at its top asymmetrically, and a lateral curvature follows. This produces the so-called sciatic scoliosis.

The postural strains of the lumbosacral region are more common in heavy women. The pain is nearly always of gradual onset and often follows a period of heavy work or a marked gain in weight.

The location of the pain is characteristic. It is not referred down the thighs or legs, but is bilateral in the low back and most acute in the lumbosacral region. It is not sharp and burning, but is described as a dull ache, or tired feeling, and is usually worse at night. These patients are frequently of the heavy type of body build with a sharp lumbar lordosis. The posture is usually poor, in that they stand with the head forward, shoulders drooped, chest flat, abdomen relaxed, lumbar spine hyperextended, body slumped and the body weight resting upon the heels with the feet pronated. A further condition frequently encountered in these overweight people, is produced by the bulky viscera in the upper abdominal cavity, eventually sagging and stretching the abdominal walls. Ventral hernia and visceroptosis ensue with their train of functional disturbances. Disabilities of the lower extremity result also from excessive weight bearing and the flat foot of middle life, when the figure has become rotund and the muscles flabby, hardly needs to be mentioned.

Undernutrition in Relation to Disease: Some General Remarks. Up to this point, I have outlined in some detail certain pathological states associated with overweight, that have impressed me of clinical interest. I now wish to make a few general remarks on our present day conceptions of the medical aspects of undernutrition and underweight.

An important phenomenon accompanying undernutrition was first demonstrated experimentally in 1906 by Magnus-Levy. He pointed out that there is a great reduction in the heat production, which takes place as an accompaniment of emaciation; in other words, the basal metabolism is lowered. Recently, it has been suggested that undernutrition depresses the whole hormonal system. Tallquist¹⁹ noted a reduction in the incidence of exophthalmic goiter in the latter years of the World War, and attributed this fact to the depressing effect of undernutrition on the thyroid gland.

Another important result of undernutrition following an insufficient diet, is a decrease in the efficiency in the performance of physical labor. This is evidenced by the fact that fatigue comes on more quickly than usual and, closely related with this reduction of physical power, mental apathy toward effort becomes apparent.

Certain mechanical changes take place as a result of the loss of body fat, causing a displacement of the anatomical position of the various organs of the body. In some individuals a loss of the subserous and mesenteric fat produces a condition in which the stomach, kidneys and the intestines are not as firmly held in position as formerly. Displacement of the heart combined with a general visceroptosis eventually follows, with the well-known train of symptoms.

All authorities agree that the undernourished individual is far more susceptible to the sensation of cold than is the wellnourished. As previously pointed out in this paper, protein causes a specific stimulus which increases heat production, whereas, carbohydrate

and fat, when absorbed in excess of the immediate requirements of the body, also cause an additional heat production. In the well-nourished, these factors are protective against the sensation of cold.

Certain important physiological facts in connection with the cardiovascular system have come to light in regard to prolonged undernutrition. Inanition reduces the number of heart beats per minute. Rubner states that in the emaciated there is a slowing of the heart rate to 60, 50, or even 40 beats per minute. The work to be accomplished by the circulation, is naturally not so great as in the wellnourished. This reduction of the burden upon the cardiovascular system is utilized by clinicians in the management of heart disease and arteriosclerosis. Benedict and others have also shown that undernutrition is accompanied by a lowering of both the systolic and the diastolic blood pressure, and this fact can also be utilized favorably, to a certain extent, in the management of essential hypertension.

During the latter part of the World War,²⁰ German observers noted that the restricted war diet tended to cause a cessation of the menses. This amenorrhea probably depended upon the great reduction of the protein of the diet, and thus represented a protective reaction on the part of the organism. War edema was another interesting form of nutritional disturbance noted in the late war; however, this condition has been described during the famines of war since the Napoleonic era. It occurred in different localities in Europe, and in some districts as high as 9 per cent of the inhabitants were affected. The disturbance appeared after prolonged inanition following diets containing predominately carbohydrate and too little protein. This type of diet tends to favor an accumulation of water in the tissues and was found to be most favorably influenced by rest and a liberal, well-balanced diet.

Undernutrition is a well-known factor in the increased incidence of certain of the infectious diseases. This was clearly shown in Germany with regard to tuberculosis. At the end of the war the death rate from tuberculosis had doubled or had reached the height which it had formerly attained before modern control over its spread had been instituted. The increased susceptibility to cold likewise increased the number of cases of upper respiratory infection and the nontuberculous pulmonary infections. It was also noted that recovery after surgical operations was more difficult. On the other hand, war nutrition, by diminishing the intake of protein and preventing overnutrition, was beneficial to many diabetics.

There are many other important medical phases of undernutrition and underweight which I shall not have time to mention, but with this short survey of some of the outstanding effects of inanition and their bearing on the problems of medicine, I shall pass to the last subject for consideration, the relation of body weight to longevity.

The Relation of Body Weight to Longevity. For knowledge concerning the effect of body weight on the expectation of life, medical men are forced to turn to insurance statistics²¹ for the most reliable data available. It is recalled that Oliver Wendell Holmes once suggested that the best recipe that he knew for longevity was to have some chronic minor ailment which one had to take care of and which required a certain amount of solicitude not to overdo things, for such people often proved eminently capable of living on beyond the Psalmist's limit of life. In view of the statistics I am about to present, might it not be well to amend this formula, and add that people should pay a little more attention to their body weight, aiming to guard against the extremes of both overweight and underweight? In recent years, the life insurance companies have laid more and more stress on the relation of body weight to the mortality rate, and I will epitomize some of their salient findings.

Among short men, that is, those below 5 feet 7 inches in height at the age period forty to forty-four years, an excess of 20 per cent in weight involves an added mortality of 30 per cent above normal. A 40 per cent excess in weight in such individuals, involves an increased mortality of nearly 80 per cent.

Among tall men, those over 5 feet 10 inches in height, the adverse situation is even more marked; for among them, at ages forty to forty-four, a 20 per cent excess in weight carries a 40 per cent increase in the mortality and a 40 per cent excess in weight doubles the mortality.

Underweight presents an entirely different picture. In general, underweight is an advantage, provided of course, the percentage is not too great. Underweight is a serious impairment in early adult life, especially among tall men.

Persons who are 5 feet 10 inches, and who are 20 per cent below the average weight for their height, show an increased mortality of 50 per cent.

Persons 30 per cent underweight have a 50 per cent excess mortality at these early ages. But from the age of forty onward there are apparently no such penalties for underweight, and this condition, in fact, becomes a distinct advantage, for these are the people who have the best mortality rates.

It would seem that the records of insurance companies indicate that there is an optimum weight, that is, a weight-height ratio in relation to age that is associated with the most favorable mortality experience, and that this optimum weight, or best build if you choose to call it, is not the average.

It is stated that those who weigh between 10 and 20 per cent below the average show the optimum condition for longevity at most ages beyond early adult life.

Discrimination must be made between types of build of overweight

persons, it being shown that among overweights having a large chest capacity, the conditions of mortality are more favorable than among those of small chest capacity. Overweights who have large trunks are better risks than those having small chests and large abdominal girths.

On the assumption that the average weight is the best weight, tables of average weights lead to the erroneous supposition that weight should continue to increase with advancing age. While this increase is of very common occurrence, the insurance records indicate that, within certain limits, this excess weight increases the insurance risk and should be carefully avoided.

The records, together with clinical experience, suggest that by restriction in diet and proper indulgence in some form of exercise conditions premonitory of organic impairment and eventual breakdown of the cardiovascular and excretory systems may be averted in many instances. At least they reinforce what hygienists have been advocating for many years and open up to the medical profession a promising field for further investigation in preventive medicine.

Conclusions. From what has been said, I have hoped to emphasize the fact that body weight is a simple measurement of extreme importance in clinical medicine. An individual who presents a marked variation in body weight should demand a rational explanation for this alteration. Our patients should be aware of this fact and unexplained variations in their weight, should incite their curiosity sufficiently to urge them to seek medical advice. Abrupt gain or loss may be explained in certain instances on a physiological basis, but it is more likely to be associated with disease.

The tendency to excessive gain in weight is best controlled in its incipency. In the majority of adults obesity is of the exogenous type and can be adequately controlled by broad hygienic measures, in which restriction in diet affords only one part of the therapeutic régime. Exceptional instances of the true constitutional type of obesity, recently studied by Strouse, do exist. They represent a true metabolic anomaly which is not entirely understood. Clear cut examples of endocrine obesity are common before the adult age and are believed to be primarily dependent on the disturbance of function of three ductless glands, namely, the thyroid, gonads, and the pituitary, either singly or combined. The endocrines *per se* play a less important part in the obesity occurring in adults.

Aside from the esthetic reasons and the constant inconvenience of marked overweight, this condition should be studiously guarded against, because of the fact that it is found to predispose to diabetes, degenerative cardiovascular diseases, arthritis and static difficulties associated with faulty bodily mechanics.

Surgery in the obese is facilitated and the mortality reduced

if an internist coöperates in the preoperative and postoperative management of these cases.

Loss of body weight and undernutrition have likewise many important medical aspects. Reduction of physical and mental vigor, increased sensibility to cold, depression of the hormonal system, lowering of the metabolic rate, and increased susceptibility to infection are among the most significant results of undernutrition.

Life insurance statistics indicate that those who weigh between 10 and 20 per cent below average, show the optimum condition for longevity at most ages beyond early adult life.

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PHYSICAL DEFECTS AS REVEALED BY PERIODIC HEALTH EXAMINATIONS.

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FROM the standpoint of individual physical efficiency and the national welfare, it is obviously desirable that the body be kept in the best possible condition to function properly. Minor, and even serious, physical impairments are often overlooked by the individual and this may later result in much personal suffering and needless loss to the community. The results of the army-draft examinations and of a large number of physical examinations of industrial employees and of school children show that this condition is considerably more common than is usually realized. It is essential that indications of physical impairment be discovered early in order that they may be corrected. Interest in this phase of health work has increased as proof has accumulated that impairments are in fact corrected and that other material benefits ensue.

The purpose of this study is not to deal further with the value of physical examinations but rather to present certain facts relative to the physical condition disclosed by those who are examined. In this study, we shall describe the principal findings in a fairly homogeneous group of 16,662 men, policyholders of the Metropolitan Life Insurance Company, examined by the Life Extension Institute in 1921. Apart from the draft examinations, this forms one of the largest groups examined in recent years under uniform conditions. An attempt will also be made to show the significance of certain interrelationships which have long been known to exist between different physical conditions. For example, it has been observed that individuals definitely above normal weight for height and age include a larger proportion who also have high blood pressure than do those whose weights are normal. Likewise, diseases of the vital organs are commonly associated with overweight. Diabetes is recognized as a frequent companion to obesity. We shall not attempt to explain the meaning of all the various interrelationships occurring in the large number of observations tabulated in this report. It seems advisable, however, to submit a somewhat detailed analysis of certain of these factors for the interest which may be derived from such a study.

1. **Source of Data.** At the outset, it should be borne in mind that this is an attempt to describe the condition of a large group of men,

* With the collaboration of Ira V. Hiscock.

supposedly able to work, as they appeared for physical examination. Obviously, data assembled in this manner have their limitations, but much effort has been exercised to present a true picture of the situation. The examinations were made by a selected group of medical examiners of the Life Extension Institute (some 8,000 in all) throughout the United States, many of whom were general practitioners new to the standards of health examinations. A fairly large proportion of the examinations (at least 20 per cent) were made by the medical staff of the institute in the New York office. Through field agents and printed instructions to its medical examiners, efforts were made to insure uniformity in the conduct of these examinations. The purpose of the examination, as outlined by the Life Extension Institute, is to determine whether or not the individual is in any way below the best possible condition of health and physical efficiency. It is to be remembered that these examinations differ radically from insurance examinations, for the individuals seeking them are desirous of a complete and thorough health survey and are very ready to disclose impairments both important and trivial in order to obtain advice and later treatment for these conditions.

Uniform reporting cards were used. The examination form is in itself an outline of instruction since it indicates under each question the line of investigation to be followed. The records of these examinations were codified and taken off on anonymous punch cards in the office of the Life Extension Institute. The tabulations of the punch cards and the statistical analysis were made by the Metropolitan Life Insurance Company as a service to the institute and to the public health movement which, we thought, would profit from the results obtained. In no case, could the tabulating office identify the individual policyholder. The strictly confidential nature of the institute's records was recognized at all times, and the statistical tables represent abstracts from the intermediary and impersonal perforated cards only.

During 1921, 18,000 physical examinations of Metropolitan policyholders were made by the institute. But of this number the records of only 16,662 examinations of white males were made available for this study. The rest were cases of females and of colored persons who were not in sufficient numbers to warrant detailed tabular analysis of their records.

The first question which presents itself for consideration is how representative those examined are of the general run of white male policyholders. This question cannot be definitely answered; but a number of points can be made to indicate certain characteristics of this group, which will help to explain some of the findings described later. In the first place those examined show that nearly 60 per cent (59.5) were over the age of thirty-four years, as compared with 53.3 per cent who were above this age in the general run of

ordinary policyholders. It is to be expected that those who seek the benefits of a physical examination would include a larger number of persons at the older ages of life when impairments make themselves more felt and when the question of prolonging life and maintaining working efficiency becomes more absorbing than it is for younger and more vigorous persons.

Unfortunately it has not been possible to secure facts of the occupations followed by this group, but general familiarity with the records, and a test run of the cards, indicated a preponderance of clerical, mercantile and executive pursuits. The regulations of the company have likewise made it much more likely that the groups would be composed of persons in somewhat better economic condition than the general run of policyholders.

If, on the other hand, this group is somewhat better constituted financially than the general run of men, it is to be expected that it is also somewhat more heavily weighted with those who are suffering from physical impairment. The examinations in accordance with the company's offer are entirely optional and it is likely that a proportion of these policyholders either knew or suspected that they were not in good physical condition and were thus more likely to avail themselves of the examination service. It is, therefore, rather difficult to say to what extent the results of the physical examinations to be set forth below show a higher proportion of defects than would be found in the community as a whole or even in the group of ordinary policyholders. But taking it altogether we do not believe that the figures are subject to any marked limitations on this score and that they will be fairly representative of what would be found among any group of 17,000 adult males examined under similar auspices.

2. Hygienic and Dietetic Habits. Further light on the composition of this group is thrown by the facts of their hygienic and dietary habits. The chief errors in personal hygiene as viewed by the examining physicians and disclosed among this group are set forth in the table on p. 579.

It is, of course, recognized that comparatively few people follow an ideal diet, and a relatively large number are guilty of errors in personal-hygiene. These facts which apply to men classed somewhere above the average among insured groups are of considerable interest from this hygienic standpoint. Our purpose, at this point, is merely to indicate the existing situation on the basis of information obtained by medical examiners and the standard and judgment of the Life Extension Institute. It will be observed that nearly two-fifths (37.6 per cent) of this group showed a high protein intake, about the same proportion (36.9 per cent) consumed too little water, a little more than two-fifths (40.7 per cent) partook of too much tea and coffee; other important errors in diet were observed in nearly one-half (46.6 per cent) of the cases. The use of tobacco in excess was found in one-third of the persons examined (33.1 per cent), and lack of exercise in three-fifths (60.8 per cent).

TABLE I.—NUMBER AND PROPORTION OF PERSONS REPORTING SPECIFIED ERROR IN HYGIENE AMONG WHITE MALE ORDINARY POLICYHOLDERS IN SPECIFIED AGE DIVISIONS.

Personal habits and conditions.	Number of cases.						Percentage of total.					
	All ages.	Under 25.	25 to 34.	35 to 44.	45 to 54.	55 and over.	All ages.	Under 25.	25 to 34.	35 to 44.	45 to 54.	55 and over.
Total persons	16,662	861	5885	5799	3023	1094	100.0	100.0	100.0	100.0	100.0	100.0
Too high protein diet	6,272	337	2274	2140	1149	372	37.6	39.1	38.6	36.9	38.0	34.0
Too little water consumed	6,142	263	2147	2184	1155	393	36.9	30.5	36.5	37.7	38.2	35.9
Too much tea and coffee	6,787	240	2222	2454	1348	523	40.7	27.9	37.8	42.3	44.6	47.8
Other errors in diet	7,766	380	2846	2712	1348	480	46.6	44.1	48.4	46.8	44.6	43.9
Alcohol excessive	111	1	32	37	31	10	0.7	0.1	0.5	0.6	1.0	0.9
Alcohol temperate	1,152	28	352	449	239	84	6.9	3.3	6.0	7.7	7.9	7.7
Tobacco excessive	5,519	239	2108	1923	967	282	33.1	27.8	35.8	33.2	32.0	25.8
Tobacco temperate	2,052	88	688	714	404	158	12.3	10.2	11.7	12.3	13.4	14.4
Hours of work too long	4,407	169	1413	1691	865	269	26.4	19.6	24.0	29.2	28.6	24.6
Lack of exercise	10,126	513	3680	3705	1760	468	60.8	59.6	62.5	63.9	58.2	42.8

3. Personal and Family History. With this primary factor of personal habits clearly in mind, it may be well to consider briefly, the family and personal histories with respect to certain important diseases, and then proceed to an analysis of defects discovered upon examination. In nearly 15,000 cases (89.2 per cent) no family history was given of the specified diseases considered important as possible inheritance factors. Some of these policyholders had not filled in the section, others had parents living, and still others reported deaths from causes not tabulated. Of the remaining 10.8 per cent of the cases, 2.6 per cent reported family history of apoplexy or arterial disease, "stroke," cerebral hemorrhage; 2.5 per cent, cancer; 1.6 per cent, tuberculosis; 1.4 per cent, nephritis or Bright's disease; 3.2 per cent, "other pulmonary diseases," with family history of epilepsy and insanity in 0.1 per cent of the cases and nervous diseases, syphilis, and other genitourinary diseases in about the same proportion.

In 69.7 per cent of the cases, no personal history of particular significance relative to disease conditions was reported. Nearly 20 per cent of the persons examined (19.4) were reported to have had rheumatism or gout, while 2 per cent (2.1) gave a history of typhoid fever. Six per cent (6.3) reported an old infection of gonorrhea and 0.5 per cent syphilis. Three per cent reported recent influenza; 0.5 per cent, ulcer of the stomach, intestines or other severe gastric disturbances; while 0.4 per cent of the cases reported each of the following: Tuberculosis, renal calculi, nervous breakdown, and neuritis. Three per cent had been operated upon for appendicitis and 2.1 per cent for hernia. The results of these family and personal histories are, we believe, of relatively little value.

4. Conditions Most Frequently Observed. It has been noted from the analysis of certain facts relative to personal hygiene that a large proportion of these people commit errors of diet, work too long hours, take too little exercise, and complain of fatigue. On the basis of a broad classification of defects found on examination, the proportion of advanced and serious defects is found to be highest at the older age groups, while minor and moderate defects are common among young men. It will be interesting to study the incidence of specific physical impairments in the broad age divisions. The chief findings, tabulated below, present an extraordinary picture of the large number and gravity of the impairments found in a group of persons who are up and about and apparently able to carry on their day's work. The findings themselves supply good reason for these examinations.

5. Posture, Build and Weight. An important factor in medical selection for life insurance is the applicant's build. A comparatively small percentage of these examined persons showed correct posture, and relatively few were of ideal weight for age and height. In this group, one-fifth (19.1 per cent) of the individuals were classed as having

TABLE II.—PERCENTAGE OF PERSONS IN SPECIFIED AGE GROUP
SHOWING PHYSICAL IMPAIRMENTS.

16,662 white males in M. L. I. Company, Ordinary Department, 1921.

Impairment.	All ages.	Under 25.	25 to 34.	35 to 44.	45 to 54.	55 and over.
Persons in specified age group { Number Percentage	16,662 100.0	861 100.0	5885 100.0	5799 100.0	3023 100.0	1091 100.0
Build, posture and weight:						
Faulty posture	19.1	16.4	16.9	19.1	20.8	29.1
Spinal curvature	5.2	7.0	4.9	5.2	4.8	5.9
Flat feet	16.4	16.8	17.0	16.6	15.4	13.7
Over 20 per cent underweight	2.4	2.0	3.2	2.3	1.5	2.1
Over 20 per cent overweight	12.9	4.9	8.1	14.4	18.9	19.8
Eyes and ears:						
Defective vision corrected	25.4	15.2	18.4	21.8	38.3	48.7
Defective vision uncorrected	29.5	28.3	28.9	30.0	29.4	31.8
Otitis media; discharging ear	1.2	2.0	1.3	1.0	1.2	0.5
Nose and throat:						
Deflected septum, slight	22.8	24.5	24.5	23.0	19.9	19.2
Deflected septum, marked	2.7	2.6	2.8	3.1	2.4	1.4
Enlarged septic or buried tonsils	26.2	34.0	32.8	25.6	17.1	13.0
Nasopharyngitis, chronic	5.5	4.9	6.0	5.4	5.0	4.4
Nasopharyngitis, acute	5.5	6.5	5.5	5.5	5.0	6.2
Hypertrophic rhinitis, enlarged turbinates	14.8	19.0	16.9	15.1	10.7	10.1
Teeth and root infection:						
Carious teeth; septic roots	8.5	6.4	7.9	8.1	9.2	13.0
Slightly infected gums	10.3	3.6	7.3	11.1	14.7	16.4
Pyorrhea, definite	4.8	1.2	2.7	5.7	7.1	7.4
Heavy dentistry, roentgen ray advised	41.8	30.0	40.7	44.2	43.5	38.8
Heart and pulse:						
Functional murmur or irregularity	6.0	6.9	5.5	5.5	6.3	9.3
Mitral murmur, stenosis	0.2	0.2	0.2	0.1	0.2	0.4
Mitral murmur, regurgitation	0.7	0.3	0.7	0.5	0.9	1.5
Aortic murmur, stenosis	0.1	...	0.1	0.1	...	0.2
Aortic murmur, regurgitation	0.1	0.1
Enlargement	2.7	1.7	2.1	2.0	3.7	8.2
Slow pulse, below 58	1.4	1.4	1.0	1.4	1.7	1.9
Rapid pulse, above 90	8.3	10.9	8.2	8.2	8.6	6.7
Intermittent pulse, extrasystoles	0.5	0.2	0.4	0.4	0.8	1.7
Bloodvessels and blood pressure:						
Normal condition of bloodvessels	77.4	89.5	83.6	76.6	71.6	55.2
Slight arterial thickening	14.3	7.2	10.9	14.9	18.2	24.0
Moderate arterial thickening	4.6	2.0	3.1	3.9	6.5	13.6
Marked arterial thickening	0.6	0.1	0.4	0.3	0.7	3.7
Blood pressure, 15 to 25 below average:	9.9	7.6	7.9	10.9	12.1	10.2
Blood pressure, 25 or more below	2.4	0.6	1.3	2.9	3.3	4.3
Normal blood pressure	80.5	86.9	85.9	80.6	74.4	62.4
Blood pressure, 20 to 40 above average	6.2	4.6	4.6	4.9	8.3	16.4
Blood pressure, 40 to 60 above average	0.7	0.1	0.2	0.5	1.1	4.3
Blood pressure, 60 or more above average	0.3	0.1	...	0.1	0.7	2.3
Stomach; abdominal organs:						
Constipation	39.7	34.6	39.5	40.4	40.1	40.3
Tenderness over liver and gall bladder	0.6	0.1	0.4	0.8	0.9	0.7
Tenderness in region of appendix	2.3	1.7	2.5	2.5	2.1	1.6
Hemorrhoids	12.3	4.4	9.3	12.8	17.7	16.3
Abdominal organs; inguinal region:						
Weak inguinal rings	5.9	5.8	5.9	6.0	5.9	5.2
Inguinal hernia, no truss	2.2	1.4	1.4	2.2	3.1	4.8
Inguinal hernia, truss worn	2.9	0.2	1.4	2.6	5.1	8.2
Varicocele	8.1	9.9	8.5	7.8	7.8	6.9
Genitourinary:						
Prostate gland, enlarged, hard, tender or boggy	3.9	1.0	2.0	3.1	5.6	15.8
Endocrine disturbances:						
Enlarged thyroid; simple goiter	2.1	3.1	3.3	1.6	1.1	0.8
Miscellaneous impairments:						
Headache	15.4	13.7	16.4	16.6	13.7	10.0
Use of patent medicines	8.8	6.3	8.9	9.5	8.5	7.4
Use of laxatives	9.1	6.4	7.6	9.1	11.4	12.6
Frequent colds	17.7	22.9	20.8	16.4	14.2	13.6
Urinary findings:						
Normal	78.3	78.6	79.9	79.5	76.0	70.1
Albumin, slight trace	12.9	12.5	12.3	12.4	14.2	15.8
Albumin, definite trace	2.4	3.5	2.4	1.8	2.5	5.2
Albumin, marked amount	0.8	1.4	0.7	0.7	0.9	1.2
Sugar, trace	3.6	4.4	3.2	3.6	4.1	4.2
Sugar, marked amount (quantitative)	0.5	0.1	0.3	0.3	1.0	1.1
Cast, granular or epithelial	0.4	0.3	...	0.5	0.7	0.8
Cast, hyaline	4.1	4.2	3.0	4.0	5.3	7.5
Indican	3.9	3.1	4.0	4.0	3.7	4.4

definitely faulty posture, while more than one-eighth (12.9 per cent) were more than 20 per cent overweight.* As would be anticipated, both of these factors increase in magnitude with advancing age. Over 16 per cent of the men were reported to have flat feet, the age periods under forty-five having the highest proportion in this respect. Those who were more than 20 per cent overweight had a considerably higher proportion of flat feet cases at age periods of thirty-five and over than did men who were slightly overweight, underweight or of normal weight. The group of foot defects, it will be remembered, were stated to be by far the most numerous of all defects found in the population of military age.¹ Flat-foot cases amounted to approximately 12 per cent (301,146 cases) of the full military population considered.

Over 5 per cent of the cases of the present study showed spinal curvature which is considerably higher than that noted for the draft examinations, but the group in the latter instance consisted entirely of young men among whom this condition would naturally be less common.

6. Overweight. Overweight is a condition associated with various physical impairments. Obviously, the habits of life which are associated with this condition are also related to other physical defects. In this discussion, we shall deal primarily with the findings for persons more than 20 per cent overweight in relation to height, assuming the average for age thirty as standard for all later years, as based on the standard height and weight tables of the Medico-Actuarial Investigation of 1912.

The data were tabulated to show the number and percentage of persons in each age period who were of normal weight according to the standard table, and the number and percentage showing specified departures from the assumed norms. An abstract of the facts for persons 5 per cent under to 5 per cent overweight (the normal group) and 20 per cent or more overweight is shown in Table III.

The percentage of normal or average weights decreased from a maximum (31.7 of persons in the specified age period) at the youngest age interval fairly regularly with advancing age. The proportion of overweights (persons 20 per cent or more above average) was 4.9 per cent at the ages under twenty-five years, and increased with advancing age.

This rising ratio of overweight with advancing age furnishes a clue to the increasing incidence of defects of the cardiovascular-renal system with advancing age. These defects indicate not only the effect of senescence, but of increasing strain upon the circulatory and renal apparatus by reason of the accumulation of adipose tissue.

* Weight and height records were taken with the coat and vest removed and the shoes on. The applicant was then stripped to the waist for the examination of heart, lungs and abdomen, and further disrobing attained with the progress of the examination.

TABLE III.—NUMBER AND PROPORTION OF (a) TOTAL WHITE MALE ORDINARY POLICYHOLDERS, (b) THOSE 5 PER CENT UNDERWEIGHT TO 5 PER CENT OVERWEIGHT, AND (c) THOSE OVER 20 PER CENT OVERWEIGHT, IN SPECIFIED AGE DIVISIONS.

Age division, years.	Number of cases.			Percentage of total in weight class for each age division.		
	All cases.	5 per cent underweight to 5 per cent overweight.	Over 20 per cent over- weight.	All cases.	5 per cent underweight to 5 per cent overweight.	Over 20 per cent over- weight.
All ages	16,662	4295	2145	100.0	25.8	12.9
Under 25	861	273	42	100.0	31.7	4.9
25 to 34	5885	1607	479	100.0	27.3	8.1
35 to 44	5799	1456	836	100.0	25.1	14.4
45 to 54	3023	697	571	100.0	23.1	18.9
55 and over . . .	1094	262	217	100.0	23.9	19.8

Among the overweights, 75 per cent (75.4) were classed as individuals having advanced or serious physical impairments requiring systematic, and in many cases, medical or surgical attention. Twenty per cent (19.6) of the overweights had moderate defects requiring medical supervision as well as hygienic correction. The normal weight group showed only 20 per cent with advanced or serious impairments, with 75.1 per cent showing moderate defects of varying degree.

The heart examinations showed no material difference between overweights and normals with respect to valve damage but there was a higher proportion of enlarged hearts (3.4 per cent) and pulse above 90 (10.9 per cent) among overweights than in persons of normal weight (2.5 and 7.1 per cent respectively).

The findings with respect to condition of the bloodvessels are of interest. Persons definitely overweight show smaller percentages of arterial thickening than do normals, and yet the proportion of persons with blood pressures 20 to 40 mm. of mercury above normal for age was 12.8 per cent among those who were overweight as compared with 5.2 per cent among normals. Whether or not this discrepancy between the proportion of persons with arterial thickening and of moderately high blood pressure may be due more to the difficulty of palpating the radial artery in stout persons than to any real difference in the actual arterial condition of persons is difficult to ascertain. While it has been believed in some circles that high blood pressure and arterial thickening necessarily go together, Allbutt,² and others have presented clinical and statistical evidence to show that they are not always associated. Allbutt also calls attention to the error of regarding arterial degeneration as a senile

disease rather than a condition or tissue change which may be due to many causes, especially infections in youth. Varicose veins were discovered in 5.7 per cent of the overweight cases and in 4.3 of those of normal weight. The proportion of cases of both normal and overweight individuals showing certain impairments of the bloodvessels is shown in the following table:

TABLE IV.—PERCENTAGE IN TOTAL OF EACH AGE GROUP OF NORMAL AND OVERWEIGHT PERSONS SHOWING SPECIFIED IMPAIRMENT OF BLOODVESSELS AND ABNORMALITIES OF BLOOD PRESSURE.

Impairments in weight classes.	All ages.	Under 25.	25 to 34.	35 to 44.	45 to 54.	55 and over.
OVERWEIGHT* GROUPS.						
Total overweights	100.0	100.0	100.0	100.0	100.0	100.0
Normal bloodvessels	79.2	97.6	87.1	80.6	75.8	61.3
Slight arterial thickening	14.1	..	8.4	15.0	16.3	20.7
Moderate arterial thickening	3.8	2.4	2.5	2.2	4.6	11.1
Marked arterial thickening	0.2	2.3
Varicose veins	5.7	..	2.1	4.7	8.2	12.0
Normal blood pressure	77.8	92.3	85.1	82.7	68.2	61.3
Blood pressure, 15 to 25 below	5.3	2.6	2.7	5.4	7.5	6.0
Blood pressure, 25 and more below	1.2	..	1.1	1.2	1.9	0.5
Blood pressure, 20 to 40 above	12.8	5.1	10.1	9.8	17.9	20.3
Blood pressure, 40 to 60 above	1.9	..	1.1	0.8	2.4	6.9
Blood pressure, 60 or more above	1.0	2.1	5.1
NORMAL WEIGHT GROUPS.						
Total normal weights	100.0	100.0	100.0	100.0	100.0	100.0
Normal bloodvessels	77.9	90.1	82.9	78.2	70.2	52.7
Slight arterial thickening	14.5	6.6	11.8	15.2	18.7	24.4
Moderate arterial thickening	4.6	2.6	2.9	3.8	7.3	14.5
Marked arterial thickening	0.6	..	0.2	0.1	1.0	4.6
Varicose veins	4.3	1.1	2.7	4.5	6.6	9.9
Normal blood pressure	81.7	86.6	87.7	81.1	73.8	62.7
Blood pressure, 15 to 25 below	10.1	7.1	7.0	11.8	14.9	9.8
Blood pressure, 25 or more below	2.2	0.7	0.8	3.1	3.0	4.3
Blood pressure, 20 to 40 above	5.2	5.6	4.3	3.4	6.8	17.3
Blood pressure, 40 to 60 above	0.6	..	0.2	0.5	1.0	3.9
Blood pressure, 60 or more above	0.2	0.1	0.4	2.0

* Over 20 per cent above standard.

This close relationship between high blood pressure and overweight is exceedingly significant, particularly at the middle-age periods. With regard to weight reduction in the management of hypertension, Rose³ states that he has observed "an almost uniform and in the majority of cases, a satisfactory reduction of high blood pressure during the process of weight reduction through dietary control. Thereby the accompanying symptoms, notably shortness of breath, palpitation, edema of lower extremities, albuminuria

(due to congestion of the kidneys), headache, distention with gas, difficult locomotion and painful feet are quickly relieved."

Overweight and Blood Pressure. In the foregoing table we found that there was a higher percentage of hypertension cases (20 mm. Hg or more above average or normal blood pressure for age) among overweights than in persons of normal weight. Certain interesting details are set forth in Table V.

TABLE V.—PERCENTAGE OF PERSONS IN EACH AGE GROUP SHOWING SYSTOLIC BLOOD PRESSURE 20 MM. HG. OR MORE ABOVE AVERAGE OR NORMAL FOR AGE.

Age division.	Overweights (20 per cent or more overweight for height and age) (a)	Normal weights (5 per cent over or under average for height and age) (b)	Difference (a-b).	Odds in favor of inherent relation.*
All ages . . .	15.7	6.1	+9.6	Practical certainty.
Under 25 . . .	5.1	5.6	- 0.5	Sample inadequate.
25 to 34 . . .	11.2	4.5	+ 6.7	Over 20,000.
35 to 44 . . .	10.7	4.0	+ 6.7	Over 15,000,000.
45 to 54 . . .	22.4	8.2	+14.2	Over 730,000,000.
55 and over . .	32.0	23.1	+ 8.9	32.

* For method of calculating these odds see Pearl, Raymond: *Medical Biometry and Statistics*, Philadelphia, Saunders, 1923, p. 218.

Note: The numbers of persons included in the several age groups are shown in Table II.

At the youngest age group the number of cases was insufficient to warrant attaching any significance to the difference in the percentage of hypertension cases found in overweights and in normal weights. But for ages beyond 25 there was practical certainty that the differences between the percentage incidence of hypertension among overweights and those for normal weights are dependably significant of the effect of overweight.

Overweight and Urinalysis Findings. A somewhat lower proportion of normal urines (74 per cent) was found among overweights than among persons of normal weight (80 per cent). More of the overweight persons showed albumin (slight trace 14.3 per cent; normals, 12.4 per cent; definite trace, 3.8 per cent; normals, 2.1 per cent; marked amount 1.2 per cent; normals 0.5 per cent). The appearance of albumin in the urine becomes marked for overweights at the older age periods, and at ages of fifty-five and over we find that a definite trace or marked amount was noted in 12.2 per cent of the cases, as compared with 6.4 per cent for the normal weight group.

For age periods of thirty-five years and upward, sugar in the urine is considerably more common among overweight people than among

those of normal weight. The incidence of casts, (granular, epithelial and hyaline), is also noticeably greater among overweight persons. While no tests were made as to the significance of the differences in the percentages of urinary abnormalities found in overweights and in normal weights, it is clear from the findings for blood pressure that for the ages beyond twenty-five, the ratios are based upon dependable numbers, and that the differences in the percentages are significant of the effect of overweight. It is clear that overweight and dietary excesses tend not only to embarrass the circulatory apparatus, but that they also impair renal efficiency.

TABLE VI.—PERCENTAGE OF (a) NORMAL AND (b) OVERWEIGHT PERSONS SHOWING SPECIFIED URINARY IMPAIRMENT BY AGE GROUPS.

Impairments in weight classes.	All ages.	Under 25.	25 to 34.	35 to 44.	45 to 54.	55 and over.
OVERWEIGHT GROUP.						
Total overweights*	100.0	100.0	100.0	100.0	100.0	100.0
Normal urine	74.0	78.0	76.8	76.0	72.5	62.9
Albumin, slight trace	14.3	9.8	12.9	13.6	14.8	19.5
Albumin, definite trace	3.8	..	3.8	2.6	3.1	11.2
Albumin, marked amount	1.2	..	1.3	0.9	1.7	1.0
Sugar, trace	4.6	2.4	2.9	4.7	6.1	4.9
Sugar, marked amount	0.9	2.4	0.7	0.6	1.1	1.5
Pus	3.3	..	3.1	3.3	3.3	3.9
Casts, granular or epithelial	0.9	..	0.9	0.6	1.3	1.0
Casts, hyaline	6.3	4.9	4.9	5.3	7.2	10.7
Indican	3.4	2.4	2.9	4.0	2.6	4.9
NORMAL WEIGHT GROUP.						
Total normal weights	100.0	100.0	100.0	100.0	100.0	100.0
Normal urine	80.0	80.2	80.9	81.7	77.7	71.9
Albumin, slight trace	12.4	12.3	11.9	11.9	13.9	14.1
Albumin, definite trace	2.1	3.2	1.9	1.7	2.0	4.4
Albumin, marked amount	0.5	1.2	0.5	0.3	0.5	2.0
Sugar, trace	3.1	4.8	3.0	2.5	3.5	3.6
Sugar, marked amount	0.5	..	0.4	0.2	0.6	2.4
Pus	2.8	1.6	2.5	2.5	3.5	4.8
Casts, granular or epithelial	0.4	..	0.2	0.3	0.9	0.8
Casts, hyaline	3.5	4.0	2.2	3.3	5.1	6.8
Indican	3.6	1.6	4.2	3.4	3.6	2.8

* 20 per cent or more above standard.

It follows, therefore, that the detection of overweight in early life and the correction of this defect through dietary and other hygienic counsel, would materially reduce the number of persons in the general population having hypertension. This would consequently postpone serious embarrassment of the circulatory appa-

tus and would eventually affect favorably the number of cardiac and renal involvements which today follow in the train of excessive alimentation.

7. Circulatory System. Physical examination revealed conditions abnormal in some degree with respect to heart and pulse in 17.2 per cent of the cases. Examiners were urged to give special consideration to cases of overrapidity or adventitious sound that might be due to nervous excitement. Functional murmur or irregularity occurred in 6 per cent, organic murmur in 1 per cent, heart enlargement in 2.7 per cent and rapid pulse (above 90) in 8.3 per cent, with slow pulse (below 58) in 1.4 per cent of those examined. These cases of heart murmur and enlargement, as might be expected, are notably more frequent among the older age groups. Slow pulse, likewise, is more common at the older ages and among low blood pressure groups. Rapid pulse, on the other hand, is higher among groups manifesting high blood pressure, and also among men under twenty-five years of age.

Abnormalities of the bloodvessels, of varying degrees, were noted in 22.6 per cent of the cases. Arterial thickening was recorded in 19.5 per cent of the cases, but only to a slight degree in 14.3 per cent. Clinical and experimental evidence^{4, 5, 6}, indicates that arterial disease, when associated with hypertension is the result rather than the cause of hypertension. Varicose veins were noted in 4.6 per cent of the cases.

Blood Pressure. The question of blood pressure in relation to overweight has already been discussed. Certain aspects of the problem of blood pressure, however, are worthy of special consideration here in view of the interest in this subject on the part of commissions, life insurance groups and public health workers. It may be stated at the outset that the blood pressure readings were usually taken with mercurial instruments, and by the auscultatory method. The life insurance standards of average blood pressure for age used by the Life Extension Institute were determined by analyses of many thousands of cases and were checked by extensive investigations in independent centers. Only 80 per cent of the policyholders included in the present study were found to have normal blood pressure according to the standards used.*

On account of the manner in which the original data were classified it is impossible to submit records of average blood pressures

* While there is still some difference of opinion concerning the relation of the factor of blood pressure to the condition of the vessels, it may be noted that high arterial pressure is believed by Barr to be the primary cause of degenerative changes in the arteries, but once these changes are established we get a vicious cycle, as they increase the work of the heart, and thus maintain the high pressure. The walls of the vessels may also be directly affected by toxins and microorganisms, such as the *spirocheta pallida* and the typhoid bacillus (Sir James Barr: *High Arterial Blood Pressure: Its Nature, Causes, Effects and Treatment*, Am. Med., 1923, 18, 349)

for different age periods. For our purposes, however, it is chiefly essential to determine by use of accepted standards clear departures from the normal. One of the most instructive studies of healthy men and women is that of Symonds.⁷ This report included 150,419 men entrants who were risks accepted by the Mutual Life Insurance Company of New York for the years 1907 to 1919 inclusive. His findings indicate that the blood pressure of healthy men of age period fifteen to nineteen, taking the average of all builds is 123.5 systolic, and at the ages of sixty and over it is 135.2 systolic.

Clinical and pathologic observations on hypertension indicate a lack of unanimity as to its etiology and pathology.⁸ Symonds states that the mortality ratios do not definitely prove that a systolic pressure of 140 mm. in the years below forty is of pathological significance, but for pressures above 145 mm. they indicate it strongly. Hunter⁹ recently called attention to the fact that persons with distinctly high pressure are prone to develop diseases of the heart, blood vessels and kidneys, the mortality from heart disease, apoplexy, and Bright's disease being very high among them. In many instances, at least, Moschcowitz¹⁰ says the pathological changes in the kidney of Bright's disease are the results rather than the cause of hypertension. Other investigators have approached the problem from the point of view of anthropometry and biophysics, emphasizing items such as vital capacity, growth type, viscosity of the blood, peripheral resistance, and so forth.

Stocks,¹¹ in an extensive statistical study, insists that from twenty to forty years of age systolic blood pressure below 98 mm. should be considered to be pathological, and below 109 mm. to be suspicious. Diastolic blood pressure does not reach its maximum at the same time as does the systolic pressure, but usually when adolescence is passed.

The data here presented relate to 13,308 cases of normal systolic blood pressure, or cases of blood pressure not departing either way from the limits of 20 mm. above or 15 mm. below the life insurance standard for the given age. In comparison with these figures there is an analysis of 1021 cases showing blood pressure ranging from 20 to 40 mm. above the average for age. The standards used for the various ages appear in Appendix Table A and have been previously reported,¹² as has the following table, taken from Dr. Fisk's original paper, but reprinted here as a background for further discussion.

These data are exceedingly interesting and, in certain cases, somewhat surprising. Literature has emphasized the importance of such items as overweight, high protein diet, the excessive use of tobacco, the existence of focal infection of the tonsils and in the dental structures. All of these, either singly or in combination, have, at times, been associated with the existence of abnormal blood

pressure,* either high or low. From these records, however, it appears that of the various factors mentioned, overweight is the outstanding one consistently accompanied by a markedly higher percentage of high blood pressure, although the condition of "heavy dentistry" also shows higher ratios.

TABLE VII.—A STUDY OF 1021 CASES OF HIGH BLOOD PRESSURE AND RELATED IMPAIRMENTS AND LIVING HABITS COMPARED WITH 13,308 CASES OF NORMAL BLOOD PRESSURE.

Physical defects and influential living habits:	Normal blood pressure, 13,308 white males (20 mm. above to 15 mm. below the standard). Per cent all ages.	High blood pressure, 1021 white males (20 to 40 mm. above standard for age). Per cent all ages.	High blood-pressure cases as compared to normal (+ or -). Differences.*
High protein diet	38.4	38.5	+ 0.1
Excess of tea and coffee	40.8	44.3	+ 3.5
Alcohol, moderate	6.9	8.8	+ 1.9
Alcohol, excess	0.6	1.1	+ 0.5
Tobacco, temperate	12.1	13.8	+ 1.7
Tobacco, excess	33.1	31.0	- 2.1
Functional heart signs	5.6	9.6	+ 4.0
Valvular defects	0.8	2.4	+ 1.6
Hypertrophy	2.2	7.8	+ 5.6
Myocardial changes	0.1	1.0	+ 0.9
Rapid pulse (90 and over)	7.7	18.7	+11.0
Arterial changes	17.8	35.2	+17.4
Tonsils, defective	26.5	26.9	+ 0.4
Caries of teeth	8.1	9.7	+ 1.6
Recession and pyorrhea	14.4	19.4	+ 5.0
Heavy dentistry, roentgen ray advised	41.4	42.7	+ 1.3
Insufficient dentistry	5.4	7.2	+ 1.8
Gastric, acid stomach, etc.	17.8	17.9	+ 0.1
Constipation	39.2	38.4	- 0.8
Albuminuria	14.7	18.1	+ 3.4
Casts	3.9	6.6	+ 2.7
Pyuria (marked or persistent)	2.7	3.5	+ 0.8
Glycosuria	3.8	5.0	+ 1.2
Overweight, 10 to 15 per cent	9.3	11.0	+ 1.7
Overweight, 15 to 20 per cent	7.5	9.5	+ 2.0
Overweight, over 20 per cent	12.6	25.5	+12.9

* No tests of the significance of these differences have been made.

Blood Pressure and Diet. Among males in this series who partook of too high protein diet,† the proportion of hypertension cases present

* While investigators agree that the immediate cause of hypertension is unknown, it has been shown by Moschowitz and others that among the remote causes, psychic factors play an important role. The importance of peripheral resistance, congenital or otherwise, in the causation of hypertension has also been indicated. (Moschowitz, E.: Congenital Peripheral Resistance: Its Causative Relation to the Precocious Hypertensive States, *Arch. Int. Med.*, 1924, 33, 566.)

† For the purpose of this classification, high protein diet is one in which meat or other concentrated protein food is taken in liberal quantities two or more times daily.

in each group is practically identical (7.3 per cent for "too high protein diet" and 7.4 per cent for all other persons). This observation is in line with previous findings by several other workers.¹³ At each of the age divisions no important differences in the percentages of hypertension cases were found as between "high protein" feeders and "all other" white males (see Table VIII). While there is some evidence that high protein diet, excess of epinephrin in the circulation and disturbances in sodium chlorid metabolism may be concerned in the production of high blood pressure, it is interesting to note that Strouse¹⁴ and Mosenthal¹⁵ found high protein diets to be without effect on the blood pressure of hypertensive cases, that Mosenthal¹⁶ states that no definite proof of a relationship of the suprarenal glands to high blood pressure has been produced, and that O'Hare and Walker¹⁷ believe that salt plays little or no role in the etiology of arterial hypertension.

TABLE VIII.—BLOOD-PRESSURE READINGS ON CASES (a) SHOWING AND (b) NOT SHOWING SPECIFIED IMPAIRMENT. 16,662† WHITE MALES, ORDINARY DEPARTMENT. 1921.

Impairment.	Total cases.		Percentage of total in impairment group with					
	No.	Per cent.	Normal blood pressure.	Blood pressure, 15 to 25 below average.	Blood pressure, 25 or more below average.	Blood pressure, 20 to 40 above average.	Blood pressure, 40 to 60 above average.	Blood pressure, 60 or more above average.
Weight:								
20 per cent or more over-weight	2,033	100.0	77.8	5.3	1.2	12.8	1.9	1.0
Normal weight*	4,251	100.0	81.7	10.1	2.2	5.2	0.6	0.2
Diet:								
Too high protein diet	6,253	100.0	81.7	8.9	2.1	6.3	0.7	0.3
Residue†	10,105	100.0	79.3	10.7	2.6	6.2	0.8	0.4
Use of tobacco:								
Excessive use of tobacco	5,466	100.0	80.6	10.4	2.4	5.8	0.5	0.3
Residue†	10,892	100.0	80.0	9.8	2.4	6.5	0.9	0.4

* Five per cent above or below average weight for age and height.

† All others not showing specified impairment.

‡ In 304 cases, blood pressure or other readings were not taken.

Blood Pressure and the Use of Tobacco. While the figures applying to tobacco users may not be conclusive, it may be noted here again that the difference in blood pressure classification between those who are listed as "temperate" and "excessive" users and as

nonusers is only slight. Temperate users are those who smoke less than 4 cigars or 9 cigarettes or 9 pipefuls daily. These observations correspond with those reported by Hunter¹⁸ in which it was stated that a moderate use of tobacco does not seem to have much influence on the blood pressure. Another check is available through the analysis of some 5520 cases of excessive tobacco users in the life extension groups,¹⁹ among whom there was no excess ratio of high blood pressure cases, although other important impairments were found such as increased ratio of arterial thickening, mouth infection, and those showing rapid pulse.

A convenient consolidation of blood pressure data for groups (a) showing a specified impairment and (b) not showing the impairment is shown in Table VIII.

Low Blood Pressure. The findings with respect to low blood pressure indicate that overweight persons, high protein eaters, had relatively fewer individuals with low blood pressure than did the normal control groups. Low blood pressure was only slightly, perhaps insignificantly, pronounced among excessive users of tobacco (see Table VIII).

8. Respiratory System. The chief interest attached to the records obtained from examination of the lungs and other respiratory organs is in the fact that 97.2 per cent were reported normal. Less than $\frac{1}{2}$ of 1 per cent of the cases (0.4) showed suspected or incipient tuberculosis, while only 6 cases were found to have the disease in advanced or moderately advanced form. Sputum examinations were not made in routine. A little over 1 per cent of the cases (1.2) had acute or chronic bronchitis and 0.4 per cent, asthma.

Conditions of the upper respiratory tract showed more striking deviations from the normal. Twenty-five per cent (25.5) showed deflected septum and 26.2 per cent enlarged, septic or buried tonsils. Only 7 cases were reported to have adenoids. Enlarged turbinates were found in 14.8 per cent of the cases.

9. Digestive System. Fifty-five per cent of the men examined showed teeth defects, 8.5 per cent of them with carious teeth, 10.3 per cent with slightly infected gums and 4.8 per cent with definite pyorrhea. These conditions were considerably higher, as might be expected, at the older age periods. As previously noted, 41.8 per cent of the cases showed that considerable dental work had been done. The data were not adequate, however, to warrant detailed analysis at each age period.

Fifty-four per cent of the individuals had some form of stomach or abdominal conditions. Constipation was reported in 39.7 per cent of the cases. This condition has been suspected of being a factor in the causation of high blood pressure, but our figures do not show any relationship in this respect. "Acid stomach" is reported in 9.8 per cent and gastric disturbances in 8.2 per cent of the cases.

Observations of tenderness in the region of the appendix (2.3 per cent), weak inguinal rings (5.9 per cent) and inguinal hernia (5.1 per cent), are of interest, as these findings are not frequently reported in collections of medical statistics.

10. Genito-urinary System. The urinalysis findings in 78.3 per cent of the cases were negative, while a slight trace of albumin was found in 12.9 per cent and a definite trace or marked amount in 2.4 per cent of the cases. Sugar was present in 3.6 per cent of the cases (marked amount, by quantitative methods in 1.5 per cent of the cases). The association between overweight and albumin and sugar in urine has been previously mentioned. Somewhat similar relationships are noted between these urinalyses findings with respect to overweight classes and those related to high blood pressure groups, although the entire significance of these findings is entirely clear. In Table VI it is noted that the proportion of cases showing albuminuria, casts and glycosuria is much higher for the high blood pressure given than among men having normal blood pressure. Evidence is accumulating²⁰ that renal and vascular lesions may be the result of hypertension rather than the cause, although until recently, hypertension was considered entirely the result of arterial and renal disease. Hyaline casts were found in 4.1 per cent of the cases and granular or epithelial casts in 0.4 per cent, and pus in 2.9 per cent. These conditions are considerably more abundant at the later age periods.

Previous history of gonorrhea was reported in 6.3 per cent of the cases. In 23.4 per cent of these cases, rheumatism or gout was reported, as compared with 19.4 per cent in the total group studied. In this group of cases, the presence of heart murmurs and heart enlargement is higher, and, as might be expected, albumin and pus in urine are more frequently discovered than in cases without such history.

11. Nervous System. There is little of interest to report relative to brain and nervous conditions as found by these examinations except that abnormalities of various grades of seriousness were reported in 16 per cent of the cases, nervousness ranking highest and sluggish or absent reflex, second.

Defective vision was reported in 54.9 per cent of the cases, with corrections in 25.4 per cent. Defective hearing was reported in 15.4 per cent of the cases and otitis media, or discharging ears, in 1.2 per cent.

12. Endocrine System. Endocrine disturbances were found in 2.3 per cent of the cases; 2.1 per cent showing enlarged thyroids.

13. Miscellaneous Findings. Chronic skin infections, such as acne, dermatitis, eczema and others, were reported in 10.4 per cent of the cases and frequent headache, in 15.4 per cent. Nearly 9 per cent (8.8) of the individuals reported the use of patent medicines. Frequent colds were mentioned in 17.7 per cent of the total cases studied.

APPENDIX A.—STANDARD OR NORM SYSTOLIC PRESSURES
(MM. HG.) AT VARIOUS AGES.

Age.	Millimeters.	Age.	Millimeters.
15 to 20	120	41 to 45	129
21 to 25	123	46 to 50	131
26 to 30	124	51 to 55	132
31 to 35	124	56 to 60	135
36 to 40	127		

14. **Conclusions and Recommendations.** It is entirely credible that the facts shown for this group of more than 16,000 males are indicative of conditions in the general population of white males. If so, it is clear that a wider extension of periodical health examinations among the adult population is indicated. Hygienic advice and the prompt treatment of both the major and minor defects thus discovered may lead to the prevention of serious consequences to these individuals later on. Most of the defects and impairments discovered in the younger ages of adult life are subject to effective control.

Perhaps the most helpful prospect is in the field of weight control. These figures show conclusively that marked overweight is associated with serious impairment of cardiovascular function, and this suggests that recognition and control of excess body weight may lead to a sharp reduction in the actual number of individuals with embarrassed hearts and bloodvessels.

The facts on hygienic habit are unique. No other data of similar scope are available in the literature. The statement of the facts under this heading ought to stimulate the extension of hygienic instruction.

Since this is a first study, too much should not be expected from the cross relationships of the data. For certain states which give premonition of serious ill-health in later life, we need more observations in order that conclusive evidence may become available for refined study. The facts on focal infection in relation to systemic disorders should be sharpened. This may be possible in physical examinations to be made in the future. The present study suggests that where we have at present mere traces of important connection between premonitory conditions and the later and graver disabling disorders, we may in the future be able to collect data which establish definite relationships.

The next important step for preventive medicine is to secure facts which will firmly establish the effective control of diseases of the heart, bloodvessels and of the renal tract. Preventive medicine will be confronted not only with the early discovery and the prompt treatment of premonitory states, but with the problem of critically testing the several methods available for the prevention of serious physical breakdown in middle and later life. It is quite possible that careful tests of the several procedures available will show which of these offers maximum results for effort expended.

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REVIEWS.

BACTERIAL INFECTION. By J. L. T. APPLETON, JR., B.S., D.D.S., Professor of Microbiology and Bacteriopathology, the Thomas W. Evans Museum and Dental Institute, School of Dentistry, University of Pennsylvania. Pp. 474; 91 engravings and 5 colored plates. Philadelphia and New York: Lea & Febiger, 1925. Price, \$6.00.

THE purpose of the author is to provide a textbook of bacteriology, with special reference to dental practice. In Part I are presented fundamentals of bacteriology—morphology and physiology of bacteria; disinfection, sterilization and classification. Both the older nomenclature appearing in classifications of Migula and of Chester, and the recent nomenclature and classification of Bergey are given. Part II deals with the nature and types of infection; with factors predisposing to infection; with natural, humeral and cellular defenses of the host against bacterial invasion; and with immunity. Part III is of value particularly to the dentist. It includes a discussion of special infections of the oral cavity and presents methods for clinical dental bacteriology.

The book fulfills its object—"to present an adequate conception of infection and a comprehensive understanding of the bearing of infection on the problems of dental practice." W. K.

INDUSTRIAL POISONS IN THE UNITED STATES. By ALICE HAMILTON, A.M., M.D., Assistant Professor of Industrial Medicine, Harvard Medical School; Formerly Special Investigator of Poisonous Industries for the United States Bureau of Labor Statistics. Pp. 590. New York: The Macmillan Company, 1925.

THIS is an excellent and very valuable book. It brings its rapidly moving subject up to date and will entirely supplant the authoritative works of a decade ago. The book is carefully compiled and written, and the presence of numerous references adds to its value.

It is interesting to note that in spite of all the increase in industrial chemical processes almost two-fifths (two hundred pages) of

the volume are devoted to lead poisoning. This will probably not long be true of such works. In the present instance it represents partly the special interest of the author and her colleagues in Boston in this topic.

The author has omitted all consideration of industrial health hazards not strictly due to chemical poisons. Thus the harmful effects of dust *per se* is not discussed, although one might feel that the title, *Industrial Poisons*, would be broad enough to include pneumokoniosis from silica. The book is by no means a complete review of occupational diseases, but is a very important contribution to the chemical phases of this subject. P.

MORTALITY STATISTICS (1922). TWENTY-THIRD ANNUAL REPORT. Department of Commerce, Bureau of the Census. Washington: Government Printing Office, 1925. Price, \$1.90.

AMERICAN ILLUSTRATED MEDICAL DICTIONARY (DORLAND). Edited by W. A. NEWMAN DORLAND, M.D. Thirteenth edition. Pp. 1344; 338 illustrations. Philadelphia and London: W. B. Saunders Company, 1925. Price, \$7.00.

THE great activity of medical science is so frequently adding new words to its vocabulary that new editions of medical dictionaries are frequently desirable. In this edition "about 2500 new words make their first appearance." I wonder how many have been dropped from the twelfth edition. Since the first edition in 1900 there have been forty-one reprints and new editions of this popular book. E. K.

THE CONQUEST OF CANCER. By H. W. S. WRIGHT, M.S., F.R.C.S. Pp. 82. New York: E. P. Dutton & Co., 1925. Price, \$1.00.

THIS booklet is one of the "Today and Tomorrow" series which has produced the well-known *Dædalus*, *Icarus*, *Tantalus* and others. It aims to present in popular manner what may be accomplished by better coöperation between the public and the medical profession toward the conquest of cancer. Believing that "the quest for a single causal factor whose 'discovery' will lead us to 'abolish cancer' is just one more hunt for the philosopher's stone" and the theory that "right living" is the best insurance against cancer today, the author tells us in plain terms what the individual should do toward insuring himself. Without accepting some of his theo-

retical dicta about the genesis of cancer, we can heartily endorse the never-too-frequently-to-be repeated principle that the public must be educated to seek expert diagnosis and treatment at the earliest possible moment. Unfortunately it must also be added that it is still necessary to educate some of the profession in the same principles.

The introduction by F. G. Crookshank, which by the way occupies one-third of the book, contains a general statement about malignant disease and a short disquisition on "the" cause of disease which could be read with profit by medical investigators in general as well as by those for whom it is here intended. E. K.

THE INTERNATIONAL MEDICAL ANNUAL. A Year Book of Treatment and Practitioner's Index. Forty-third year. Pp. 548; 43 plates and 87 illustrations. New York: William Wood & Co., 1925.

APART from the criticism applicable to year books in general, the overemphasis placed upon the new, radical and evanescent, there is little but approbation which can be said for the forty-third issue of the *Medical Annual*. It gives an excellent summary of the progress of the year in medicine and surgery as interpreted by a staff of twenty-eight contributors, many of whom are men of international eminence. The alphabetical arrangement of the subjects is a helpful feature of this work which will appeal to the practitioner, as will also the emphasis which is placed upon treatment.

A.

GOITER: NONSURGICAL TYPES AND TREATMENT. By ISRAEL BRAM, M.D., Instructor in Clinical Medicine, Jefferson Medical College, Philadelphia. Pp. 479; 152 illustrations. New York: The Macmillan Company, 1924.

A PRESENTATION of thyroid disease by a man who does not believe in the surgical treatment of exophthalmic goiter, but prefers rest and medical measures. So far, so good; but the extremeness of the author's views, a prolix, rambling style with endless repetition, and not a few statements scientifically inaccurate hopelessly outbalance some good clinical observations. Surgery is dismissed with "to say the least, the prognosis of Graves' disease under surgical treatment is hardly better than if the patient were left alone to take his chances with spontaneous recovery." Of questionable, unproven or erroneous propositions are such: That "leukopenia is to be regarded as pathognomonic of Graves'

disease;" that a flesh diet is potent stimulation to endocrine dysfunction, causes goiter and therefore a meat-free diet is imperative in *simple* goiter; that "ordinarily the ingestion of 100 gm. of sugar causes no increase in the normal individual's blood (sugar). . . . In hyperthyroidism this quantity increases the normal content to about double;" that the basal metabolism is routinely increased in diabetes mellitus. Again under the section of the treatment of Graves' disease are advised: Pancreatic extract by mouth for glycosuria; ichthyol for the cardiac symptoms; routine injection of horse serum before parturition to prevent bleeding; while quinin, the author's favorite drug, is said to counteract the excess of iodine in the blood; electrotherapy is much extolled. R. K.

MEDICAL AND SURGICAL REPORT OF THE ROOSEVELT HOSPITAL, NEW YORK. Pp. 378; 47 illustrations. New York: Paul B. Hoeber, 1925.

AFTER a lapse of ten years the second *Medical and Surgical Report of the Roosevelt Hospital* now makes its appearance. In addition to reprints of articles which have appeared in various medical and surgical journals, the *Report* contains articles which have been written expressly for this work. The names of Dowd, Dwight, Floyd and Peck are attached to sixteen of the thirty-four papers. J. A.

A TEXT-BOOK OF GENERAL BACTERIOLOGY. By EDWIN O. JORDAN, PH.D., Professor of Bacteriology in the University of Chicago and in Rush Medical College. Eighth Edition, thoroughly revised. Pp. 752; 179 illustrations. Philadelphia and London: W. B. Saunders Company, 1924.

It is pleasing to note the biennial regularity with which new editions of this excellent text-book of general bacteriology appear. Years of use as a text for teaching have added refinement and perfection of presentation through seven careful revisions.

The present eighth edition contains new material on the bacteriophage phenomenon, tularemia, botulism, scarlet fever, and other subjects in which recent progress has been made. J. S.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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Parenchymal Rales in Pulmonary Tuberculosis: Their Clinical Significance.—One of the most puzzling and difficult problems of physical diagnosis is the proper interpretation of the rather small moist rale, elicited by coughing, heard over the chest of the normal individual at times, but most frequently over some area of pulmonary tissue that may be the seat of an active lesion or the location of a preëxisting process now inactive, or rather incapable of producing symptoms. As BRUNS (*Jour. Am. Med. Assn.*, 1925, 85, 739) remarks, rales of this type are generally accepted as important signs of chronic parenchymatous tuberculous lesions. Furthermore, these rales are usually considered to be the result of moisture in the terminal bronchioles. That such is not the case, the author attempts to show by a process of clinical deduction and by a study of lungs removed at autopsy. Both methods of study are open to serious objections, particularly the latter method of removing the lungs, inflating them with bellows, observing where rales are heard through the auscultatory stethoscope and then sectioning this area for evidence of moisture, pneumonia, congestion or tubercle. Gross evidence of disease would be observed, but the method is not sufficiently refined to determine the presence or absence of moisture in the smaller bronchioles or alveoli. Therefore it cannot be proven by this method that these so-called indeterminate rales are produced by the sudden opening of collapsed lobules and that moisture is not present in the alveoli. The author's contention that these rales are atelectatic in origin is a belief that is held by many internists, and despite the criticism of his method of proving

his case, the procedure he employs is probably as accurate as any devised up to the present. That portion of the paper which deals with the author's clinical cases seems to the reviewer to contain the real meat of his presentation. He calls forcible attention to the fact that indeterminate rales may exist for years in individuals who are apparently in every other respect normal and buttresses his arguments with 5 well-selected cases. The author will have performed a real service if he is able to correct the very general misconception of the genesis of rales of this character and can impress upon the physician the fact that such rales do not necessarily mean tubercle without confirmatory proof from the history, symptoms, laboratory and roentgen-ray examination.

Plague: Past, Present and Future.—The most interesting observations made by LLOYD (*Jour. Am. Med. Assn.*, 1925, 85, 729) have to do with the laboratory diagnosis and the treatment of plague. He speaks from an experience, which incidentally must have been appalling, which includes the management of 1491 cases occurring in Guayaquil, Ecuador, during a period of two years. In order to make a bacteriologic diagnosis of plague from postmortem tissue, the author recommends the following procedures: Inoculate 3 guinea pigs, 1 intraperitoneally, 1 subcutaneously and the third by rubbing the infected material on the clipped unbroken skin of the abdomen with the flat side of a dull knife. This latter method is the best in order to procure a pure culture of the *Bacillus pestis*. The growth is subsequently transferred to a moderately dry agar slant and to bouillon, where it presents certain typical characteristics. In the treatment of plague only one method merits serious consideration—the use of fresh antiplague serum in doses of 80 to 100 cc. initially, with succeeding doses of 40 cc. every twelve hours until all danger is passed. The author writes that he is mindful of the fact that antiplague serum is looked upon with great skepticism by many prominent men in the United States, but he expresses himself unequivocally in favor of this method of treatment, provided that fresh serum is given early in the course of the disease in large doses.

The Prognostic Value of Differentiating Immature Neutrophils in the Blood.—This very short paper is of interest because it recalls to our mind the necessity of making a careful morphologic study of the white cells, when making a differential count of the leukocytes in those conditions in which the microscopist is usually expected simply to report upon the percentage of polymorphonuclears present in the blood smear. DE COURCY and THUSS (*Ohio State Med. Jour.*, 1925, 21, 487) detail the blood counts in 10 cases of sepsis, and show that the presence of immature forms of neutrophils in a ratio greater than 3 or 4 per cent is of decidedly bad prognostic import, and that the higher the percentage of the young forms rises the more serious is the prognosis. They use Schilling's classification of young cells: (1) Cells smaller than myelocytes, with a single deeper staining nucleus than in the myelocyte, round and often slightly indented; (2) staff-shaped single nucleus staining deep, deeply indented in shape of horseshoe and often having the appearance of the letter S.

The Vital Capacity of the Lungs in Relation to Clinical Medicine.—ARNETT (*Boston Med. and Surg. Jour.*, 1925, 193, 157) gives an excellent review of the present-day knowledge of the vital capacity of the lungs. He brings out one point which properly could bear repetition and accentuation: Routine determination of the vital capacity of the person in good health should be advised because if this is known, and as there is no known standard except that of the individual, variations from this standard will be of value in determining early cardiac and pulmonary disease.

Cases Illustrating the Indications for the Use of Quinidin Sulphate in Heart Disorders.—WHITE and SPRAGUE (*Boston Med. and Surg. Jour.*, 1925, 193, 91) present a clinical paper with a report of 15 cases of heart disease treated by quinidin sulphate in order to illustrate the type of case in which quinidin is of value and the type in which it is valueless, or even harmful. The authors point out that so much has been written concerning the dangers of the drug that medical men have become most timorous in making use of a drug that has a very real worth. To illustrate their point they quote in detail 2 cases of paroxysmal auricular fibrillation, 1 case of paroxysmal tachycardia and 5 cases of resistant auricular fibrillation. The 7 cases in which quinidin was valueless include 1 in which the drug was given in large amounts without proper supervision of the patient, 2 in which the indications were doubtful, 1 in which there was extensive heart disease, 1 other in which there was congestion failure and, lastly, 1 of those rare cases in which the drug caused the patient to have marked evidences of cinchonism. The three most important contraindications to the drug are a history of congestive failure, extensive heart disease and sensitiveness to the drug.

SURGERY

UNDER THE CHARGE OF

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Massive Excision of Subcutaneous Abdominal Fat.—HEINECK (*Virginia Med. Month.*, 1925, 52, 106) states that in suitably selected cases the operative removal from the abdominal wall of large, wedge masses of subcutaneous fat has the following advantages. It is a safe and invariably beneficial surgical procedure. (It has always been performed under general anesthesia.) It is always devoid of immediate or remote dangers to the patient. Although the wound is extensive, the hemorrhage is moderate and healing is good. It is simple

of execution, and if unassociated with another operative procedure the technic is easy and the performance of the operation does not consume much time. It is all important that the incisions be carried to but not beyond the fascia. It is not infrequently employed in conjunction with other operations. It eliminates a physical handicap, effects a marked improvement in the patient's appearance and general well-being and procures complete relief from an unsightly painful and disabling deformity.

Roentgenoscopic Evidence of the Association of Ureteral Stricture and Urinary Calculus.—HUNNER (*Jour. Urol.*, 1925, 13, 497) says that the presence of a calculus in a kidney or ureter is presumptive evidence of a coëxistent ureteral stricture. Ureteral stricture is probably of blood-borne origin. It is practically always bilateral. The symptoms and many of the pathologic changes which were formerly ascribed to the presence of a stone are probably more often the result of stasis due to the stricture. Such phenomena as silent stone, renorenal reflex, calculous anuria with a stone obstructing on one side only, the frequent recurrence of stone on the side operated upon, the frequent postoperative development of stone on the opposite side, the recurrence of symptoms soon after operation—all can be explained in a more logical way. Many stones are silent, but the accompanying ureteral stricture is not often without symptoms. Reflex anuria, heretofore considered a nervous phenomenon, will likewise be found in most instances to be due to bilateral stricture and to depend on actual physical changes in the narrowed areas of both ureters.

The etiology of urinary calculus formation has been discussed in which the evidence for and against such theories as the chemical, microbic and the mechanical or urinary stasis theories have been set forth. No single theory is all-sufficient for the explanation of such a complicated problem as that of calculus formation. If, however, ureteral stricture can be demonstrated in approximately 100 per cent of the cases with stone in the kidney or ureter, it is evident that a new angle from the etiologic point may be taken.

Spastic Obstruction to the Ureters.—HEPBURN (*Ann. Surg.*, 1925, 81, 1133) states that he is surprised that so little consideration has been given to the possible influence of the circular muscle rings found in the walls of the drain pipes of the urinary system. Physiologically the ureters conduct the urine from the renal pyramids by a peristaltic action similar to that of the alimentary tract. This contraction is seemingly independent of content and nerve supply. The first observation bearing on this hypothesis is that obstructions to the ureter are most commonly found at the following places: The ureteropelvic junction, at the point where the ureter goes over the iliac vessels, in the broad ligament portion in females and in the intramural or trigonal portion. Every one of these places is the location of a circular muscle band. The commonest point of obstruction is in the intramural portion. Not only is this group of circular fibers largest here, but they here practically become a part of the trigone and the two ureteral openings are connected by the interureteric muscle band. The diagnosis of ureteral obstruction due to interureteric muscle spasm is made

from history, the cystoscopic appearance of the interureteric muscle and from the ureterograms. Cutting the interureteric muscle and closing the cut anteroposteriorly in conjunction with dilatation of the intramural portion of the ureters with bougies is the best treatment for those cases that will not yield to hygiene or dilatation with bougies.

The Surgery of Hypertrophic Pyloric Stenosis.—ZIEROLD (*Minnesota Med.*, 1925, 8, 393) says that it is probable that complete closure of the lumen rarely, if ever, occurs and that some portion of the feedings passes onward into the intestine, the resulting stool being more scanty than normal. This finding of persistently small bile-stained mucous stools is of the greatest significance, as it at once gives information as to the location and the severity of the lesion. Continued vomiting, accompanied by visible gastric peristalsis and starvation stools, implies failure of the stomach to empty, and if not promptly and effectively relieved by other means, is an indication for surgery. Gastroenterostomy, the operation of choice up to 1911, has been definitely discarded as unphysiological and dangerous. Today the generally accepted procedure is that of Rammstedt, either in its original form or as modified by Strauss. The fate of the tumor has been the subject of numerous investigations, of which Wollstein's are the most complete. In a histologic study of the pylorus in 25 infants, who died at various times, following operation, she found that a regular involution of the muscle occurs. Sixteen months after operation only a faint line is seen, and at two years the scar is scarcely visible.

Skeletal Traction.—MOORHEAD (*Am. Jour. Surg.*, 1925, 39, 113) claims that skeletal traction has demonstrated itself as a useful and safe procedure in certain recent fractures, particularly that group in which reduction and maintenance has hitherto demanded open correction with or without the use of nonabsorbable material, such as plates, wires, screws, bands or clamps. Certain fractures of the femur, notably the supracondylar group are in many cases irreducible, except by open operation or skeletal traction. The latter is preferable, because it is safer and simpler. This procedure of skeletal traction has wide application in compound fractures, because the traction medium can be introduced at a distance from the wound and further because the necessary dressings can be unhampered, inasmuch as splintage is reduced to the minimum. The limb can be readily inspected and the method lends itself to mobilization of the entire musculature and adjacent joints. Skeletal traction with osteotomy through the fracture line replaces extensive operations in malunion and is a welcome substitute for bone reshaping or bone sacrifice, with or without metallic suturing.

The Surgical Treatment of Cancer of the Breast.—JUDD (*Am. Jour. Roentgenol. and Rad. Therap.*, 1925, 13, 411) believes that good results from surgical treatment of cancer of the breast depend more on early operation than on extensive procedures. Some of the early cases start with a high degree of malignancy and will recur in spite of early and radical treatment, while some of the fairly advanced cases, because they are of a lower degree of malignancy, will be cured by operation.

Cancer probably originates in a single focus; the avenues of its extension from the mammary gland are well understood. A radical operation in which the adjacent fascia, muscles and lymphatics are removed is essential in all operable malignant cases. But in spite of this procedure there will be early recurrences in certain apparently favorable cases. On the other hand, many patients in whom the disease is obviously extensive will remain well. In estimating the result of treatment for cancer of the breast it is obviously necessary to take into consideration the type and grade of malignancy dealt with. In a series of cases in which the malignancy is of low grade the results are sure to be better than in one composed almost entirely of highly malignant cases. There is very good evidence of the beneficial effect of radiotherapy alone in certain cases, including those in which recurrences have followed surgery, but there is every reason to believe that some combination of surgery and radiotherapy can be found which will do more than either alone.

Gonorrhea of the Epididymis.—GRANT (*Urol. and Cutan. Rev.*, 1925, 29, 285) states that the treatment of epididymitis itself is a surgical procedure. Where the gonococcus has invaded the epididymis the most important factor consists in killing the gonococcus. The therapeusis of epididymitis is not a simple matter. It is almost impossible to reach this structure through the posterior urethra and ejaculatory ducts by the injection of drugs in solution. It is questionable whether any good is accomplished when the vas deferens is opened surgically for injection of some germicidal drugs. It has seemed that the gonococcus is an organism which is destroyed particularly easily by the application of heat. For example, if heat can be applied in such a way as to reach the gonococcus at a temperature of 112° F. for five minutes' exposure it is practically certain that the organism will be destroyed. The author has adopted the method advocated by Corbus of Chicago. The principle is to force heat into the epididymis itself at 106° to 108° F., continuing the application for thirty to forty minutes, which practically destroys all gonococci present. In order to do this two electrodes must be used through which the electric current passes and the heat accumulates in the center between these two electrodes. This method was used in a series of 35 cases of gonorrheal epididymitis. Only 1 patient failed to respond as promptly as is the rule. In this case there was a hydrocele of long duration. After it was tapped and heat applied to the epididymis a second time the patient was completely relieved.

Some Problems in Anorectal Surgery.—ZOBEL (*Am. Jour. Surg.*, 1925, 39, 119) claims that individuals suffering from rectal trouble usually come to the surgeon complaining of one of the following symptoms: Pain, bleeding, itching or protrusion. Complaint may also be made of constipation, diarrhea or of a discharge of pus or mucus. In the majority of cases pain is found to be due to an anal fissure. In many of these sufferers, added to their pain, is the conscious or subconscious fear that the trouble may be a rectal cancer. As a matter of fact it may be safely stated that when there is severe pain in the anorectal region one rarely finds a cancer. As a rule, there is pain with

hemorrhoids only when they are eroded and inflamed or are thrombotic. A complete fistula causes little if any pain, except when its external opening closes. It is then practically an abscess. The author thinks that good judgment must be exhibited before an operation for the extirpation of a rectal cancer is advised. The patient's age, physical condition, circumstances and environment, the situation and duration of the growth, among other things, must be taken into account. In patients over sixty years of age, with a growth present for sometime, colostomy is advised, followed by massive roentgen-ray doses. The author has not drawn his final conclusions as to the value of the latter. In those under this age an extirpation of the growth should be attempted if there be even a fair chance for a good result. The two-stage or three-stage operations, with preliminary colostomy, give the best results as regards mortality. The use of radium is not advised.

Management of Intracranial Injuries with or without Fracture.—CONNORS (*Ann. Surg.*, 1925, 81, 901) states that no case of intracranial injury should be operated upon until definite localization of the brain injury has been determined. If an operation is to be performed it should expose the brain laceration, remove the compressing substance and control hemorrhage. The subtemporal decompression operation as a routine measure fails in the majority of cases, because it does not expose the lacerated brain, remove the compressing substance or check the hemorrhage. In view of the fact that such an operation has not yet been demonstrated, palliative treatment is recommended in cases of *contre-coup* laceration of the brain.

Gastric Ulcer and Gastric Carcinoma: An Inquiry into Their Relationship.—DIBLE (*Brit. Jour. Surg.*, 1925, 12, 666) says that his study shows that gastric ulcers coming to operation as such prove on their removal to be simple in nature almost invariably, and that gastric carcinomata, as far as can be judged by histologic evidence, are in a large majority of cases malignant from their inception. This is not a denial of the possibility of malignant change supervening in a chronic gastric ulcer. It is a conservative view of the frequency of this event. Experimental work in a variety of fields has clearly shown the tendency for a supervention of malignant diseases in sites of constant irritation of a certain grade. Malignancy may supervene in a chronic ulcer of any type, but apart from the continued applications of certain known irritants, it is not a common event. It may be conceded that a gastric ulcer, by virtue of its chronicity and constant exposure to the gastric juice, is more likely to be prone to malignant change than a simple ulcer in another situation. This is conceded, but it does not affect the conclusion that this change is not a common one. Gastric carcinomata occur most frequently closely to the pylorus. They may occur in the ulcer site, but it is not their commonest position. The history of gastric ulcer is long, while that of carcinoma is short. This diagnostic fact, so much emphasized by past generations, seems almost ignored by some of the modern schools. In the author's cases the average length of the history in the 108 cases of chronic ulcer, proved histologically in which this information was available, was ten years and four months, whereas the average length of history in the 28 simi-

larly proved cases of carcinoma was only two years and three months. The average age of his cases of ulcer and carcinoma at the time of operation is forty-four and forty-nine years respectively. When the duration of symptoms in the two conditions is taken into account the average ages of onset are found to be more widely separated, being thirty-three and forty-five years respectively.

THERAPEUTICS

UNDER THE CHARGE OF

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The Cure of Cardiac Fibrillation.—WENCKEBACH (*Thér. d. Gegen.*, 1925, 5, 199) calls attention to the fact that there is no unanimity or opinion regarding the use of quinidin in cardiac fibrillation in spite of the large amount of work which has been done on this subject, and reviews the indications and contraindications for its use. He emphasizes the fact that quinidin is a cardiac depressant, and its action is antagonistic to the action of digitalis. On this paralyzing action rests the therapeutic use of quinidin in cases of cardiac extrasystole, tachycardia, flutter and fibrillation. In treating cardiac disease with this drug one must constantly remember these fundamental facts, and refrain from using it on patients with severe heart disease and extensive myocarditis. In his experience the author has found that it is useless and often harmful in those cases where by the use of digitalis therapy there is no improvement in cardiac action or circulation. In such cases the auricular fibrillation is responsible for only a small part of the circulatory disturbance, and to give the patient a drug which has a depressing action on the heart muscle should be avoided. The patients who have severe valvular disease, and particularly those with mitral stenosis and auricular fibrillation, should be given quinidin with great care. Because of the dilatation of the left auricle in these cases, and the stagnation of blood in this cavity, thrombi frequently form in the left auricular appendage. When the cardiac action becomes regular embolism may result from mobilization of these thrombi. Such a possibility does not contraindicate the use of quinidin in these cases, but a roentgen-ray will show marked dilatation of the left auricle and inform the physician if such a possibility must be considered. The chief indication for quinidin therapy is in treating those patients whose health and circulation are upset by the complete cardiac irregularity and whose heart muscle is in comparatively good condition. In such cases good results can be expected, for the fibrillation of the auricle is the main cause of the symptoms. It is important to watch the blood pressure when giving quinidin, for it lowers arterial tone, and should not be used in large doses on patients with low blood pressure. Cases of exophthalmic goiter can tolerate large doses of quinidin, and the

effect is to reduce the general overactivity of all bodily functions. It is useless to force or continue quinidin with those patients whose fibrillation returns after a few days or a week. Adaptation of the circulation to sudden or frequent changes of cardiac rate is hard for the patient, and it is better to regulate ventricular action by administration of digitalis. Before giving quinidin to cure auricular fibrillation, the patient should be put to bed and a test dose given of 0.25 gm., to find out if the patient has an idiosyncrasy to quinidin. If this amount is well tolerated the patient is given from 0.25 to 0.4 gm. four times a day. Occasionally normal heart rhythm is established in twenty-four hours; usually the cure lasts longer, even as long as ten days. Personal observation of the patient is essential, and if there is a marked fall in blood pressure, or if the patient complains of weakness, this treatment should be discontinued. In cases with dyspnea or signs of stasis from cardiac insufficiency a digitalis course should precede the quinidin course. To those patients whose hearts show only a slowing of rate and diminution of the arrhythmia after a course of quinidin one should give a course of digitalis therapy. When the ventricular rate has reached 70 or 80 beats a minute digitalis should be discontinued, and quinidin then will aid greatly in the treatment. There is no contraindication to the use of quinidin with digitalis in an attempt to effect ventricular action without attempting to cure auricular fibrillation. On the contrary, the older practitioners combined quinin and digitalis, and it was observed that patients so treated could tolerate larger doses of digitalis. Doubtless quinin in this respect is a welcome addition to our methods for reestablishing a normal heart action.

Luminal in the Treatment of Epilepsy.—OSTMANN (*Deutsch. med. Wchnschr.*, 1925, 15, 605) advocates the use of luminal in the treatment of epilepsy, and has avoided harmful effects from the use of this drug by withholding it from patients with high blood pressure and striking vasomotor disturbances. New cases he treats with 0.05 gm. of luminal given three times a day, and increases the dose by 0.05 gm. until attacks are under control. When this has been accomplished the successful dose is continued for four weeks and then gradually reduced by the same amount. Should epileptic symptoms appear again this dose must be increased until they are kept under control. Institutional cases were treated with the same object in view and the dose which was successful in controlling attacks was continued for ten days and then gradually reduced. When symptoms appeared the dose was gradually increased to the amount which controlled them and continued for ten days, when the smallest amount which controlled attack was determined. This was continued for a month. Usually this class of patients required 0.2 to 0.3 gm. of luminal a day, which was divided into three doses. Never was more than 0.6 gm. a day given. If results were not obtained with luminal alone it was combined with bromid. Luminal is not a specific drug in the treatment of epilepsy, but many cases were relieved, and of 30 cases treated by the author 28 were benefited, and 12 of these cases were able to work as long as they took the luminal.

Treatment of Vascular Filariasis.—TANON (*Presse méd.*, 1925, 17, 265) has employed the arsenical preparation hectin for fourteen years in the treatment of filariasis, and reports not only amelioration of symptoms but permanent cures. In all cases where the embryos were present in the blood before treatment they quickly disappeared and the subjective symptoms gradually subsided. The majority of cases even after returning to the tropics had no relapse or return of filariasis. The technic consists of the subcutaneous or intramuscular injection of 0.2 gm. of hectin every other day for twenty days in cases which show at least one embryo in a microscopic field, and 0.1 gm. if less are found. A second series of ten injections is given after an interval of twenty days, using 0.1 gm. at each injection, given twice a week whether embryos are present in the blood or not. In the cases with elephantiasis general treatment has little or no effect on the local lesion, and massage and elastic compression is advised. Hectin has the advantage over other arsenicals which have been used in the treatment of filariasis, in that it is harmless. The author reports that he has never seen ocular disturbances or toxic manifestations from its use.

A Method for the Immediate Treatment of Salvarsan Infiltration.—DIETEL (*München. med. Wchnschr.*, 1925, 55, 128) has found that the pain can be quickly controlled, and the infiltration caused by subcutaneously injected salvarsan relieved by immediate injection of 10 cc. of sterile physiologic saline solution. Aspiration alone of the salvarsan solution does not relieve the pain caused by the solution, and often there results an extensive inflammatory reaction. When necessary he aspirates as much of the salvarsan solution as possible, and immediately injects at the site of infiltration 10 cc. of sterile saline solution which not only dilutes the salvarsan solution in the tissues so that inflammation does not result, but the larger amount of sodium chlorid solution causes a more rapid withdrawal of the infiltrated salvarsan.

The Action of the Intravenous Injection of a Solution of 40 Per Cent Urotropin.—Since VOGT (*Zentralbl. f. Gynäk.*, 1921, 45, 49) first advocated the intravenous injection of an aqueous solution of urotropin for the treatment of urinary retention this treatment appears to be the method of choice. RITSCHER (*Deutsch. med. Wchnschr.*, 1925, 19, 776) used this method in the treatment of 69 patients with urinary retention, and reports success in 94 per cent of cases. This method was used to give relief to patients suffering with postoperative retention, and also to relieve retention which occurred several days after operation, which was of nervous origin. The usual procedure was to inject 5 cc. of a sterile aqueous solution of urotropin on the evening after operation if necessary, and if no relief followed to repeat the same dose in an hour and a half to two hours. If catheterization was then necessary the danger of infecting the bladder was minimized. Sterile solutions of urotropin are prepared by the firm of E. Schering, and sold in ampules containing 5 cc. This solution must be injected intravenously for subcutaneous infiltration is followed by painful local inflammation.

PEDIATRICS

UNDER THE CHARGE OF

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Insulin in the Treatment of Malnourished Infants.—TISDALL, BROWN, DRAKE and CODY (*Am. Jour. Dis. Child.*, 1925, 30, 10) studied the effect of the administration of insulin to malnourished infants. Nine infants received insulin in conjunction with the intravenous injection of 20 per cent glucose. Seven infants over a total of thirteen periods received insulin in conjunction with 15 per cent of glucose subcutaneously. Two infants received insulin in conjunction with 10 per cent glucose subcutaneously and 6 infants in conjunction with the feeding. A definite increase in the weight was obtained in 50 per cent of the cases. In these cases in many instances two factors were present which lessened the probability that insulin was the cause of the increase in weight. The intravenous injection of 20 per cent glucose and insulin together is probably not the most efficient method of administration. Insulin apparently produced the most marked diminution in the elevation of the blood sugar when administered about one and one-half hours before the glucose. The effect of the insulin on the blood-sugar concentration varies tremendously in different infants, consequently its administration is not without danger. Certain infants may have a very marked hypoglycemia without showing any hypoglycemic reaction. No positive evidence was obtained that insulin of itself, when administered with carbohydrate to undernourished children produces any beneficial effect.

Anemia in a Newborn Infant.—SANFORD (*Am. Jour. Dis. Child.*, 1925, 30, 19) reports a case in which there was a marked anemia in an apparently healthy newborn infant at birth. The blood showed evidence of extreme activity, such as high white cell count and nucleated red blood cells, with poikilocytosis and polychromasia, and decreased blood-platelet formation. There was no evidence that there was an increase in blood destruction, for the jaundice which appeared on the second day and disappeared on the fourth occurred during the improvement of the blood picture and normal bleeding and coagulation time. The van den Bergh test for hepatic bilirubin was positive, suggesting this jaundice was of hepatic origin. During this time the liver also decreased in size. The spleen steadily decreased in size as the blood picture improved, and this occurred without treatment of any kind, unless the roentgenogram of the extremities was in some sense a factor. The increase in hemoglobin continued more rapidly than the increase in erythrocytes, and the color index was kept over rather than under 1. It was known that the mother's blood picture was normal at the time of this delivery, and also that the older brother's blood was normal. There was no family history of syphilis, tuberculosis, debility or mis-

carriages. The factor of a maternal influence must, therefore, be ruled out. No explanation of the before-mentioned condition can be offered. The child's recovery was rapid and complete without treatment in any way—except for the slight exposure to the roentgen ray.

Gastric Analyses in Normal Infants and in Those Convalescent from Diarrhea.—DAVISON (*Am. Jour. Dis. Child.*, 1925, 30, 23) states that the presence of swallowed saliva or of regurgitated duodenal material is an important factor in reducing the gastric acidity of normal infants and of those convalescent from diarrhea, and also in determining to some extent the types of organisms found in gastric contents. Less than one-third of the specimens of gastric contents of these infants were free from salivary or duodenal contamination. Diets of some form of lactic acid milk increased the gastric acidity, but there was very little evidence that either these diets or the increased gastric acidity resulting therefrom destroyed many organisms in the stomach. The acidity of specimens collected less than six hours after a meal was higher than that of specimens collected later. This difference may have been due to the fact that all of the specimens collected later than six hours after a meal contained saliva. Elevation of the body temperature decreased the gastric acidity but this change can possibly be explained by the frequency with which the gastric contents of febrile infants was contaminated with saliva. The presence of vomiting increased the gastric acidity. Practically no difference could be found in the reaction or cultures of the gastric contents of normal infants and of those convalescent from diarrhea. As reported in a previous contribution the author found that the more acid the gastric contents, the greater the acidity of the duodenal contents obtained less than one-half hour later. The reaction of the gastric contents did not have any apparent relation to the amounts of duodenal amylase and trypsin. This observation does not agree with the usual physiological conception that the acidity of the gastric contents stimulates the flow of pancreatic juice, bile and intestinal secretions. Duodenal cultures were more frequently sterile in infants whose gastric acidity was from pH 5.1 to 5.7 than in those in whom it was from pH 3.6 to 4.4. No observations were made on the relationship of the psychic state of the infant and the results of the gastric analyses, but it is possible that any form of excitement may affect the gastric secretion. All of these factors should be taken into consideration before conclusions in regard to the gastric secretion can be drawn from analyses of gastric contents in infants.

Tuberculosis in Children.—DROLET (*Am. Rev. Tuberc.*, 1925, 11, 292) reveals that during the last twenty-six years in New York City 28,762 deaths from various forms of tuberculosis have been reported among children under fifteen years of age. In 1898, 1370 such deaths were reported among a total childhood population estimated at 1,002,767. In 1923, with a child population increased by more than 675,000, the tuberculosis death rate was reduced to only 547. The former death rate of 136 per 100,000 was reduced to 33, or by 76 per cent. In children under fifteen years of age tuberculosis meningitis causes one-half of the deaths. The death rate from this cause in

children in New York City has been reduced from 78 to 17 per 100,000, or by 78 per cent, between 1898 and 1913. In this group of children pulmonary tuberculosis is the next important type after the meningeal form, and nearly one-third of all of the tuberculosis deaths among children were of this form. The death rate which was 31 per 100,000 was reduced to 10, or by 68 per cent. Pulmonary tuberculosis, though it has greatly decreased in New York, has not been reduced quite as fast as the other forms. The abdominal type of tuberculosis in children under fifteen years of age in New York City, though causing a large proportion of the deaths, showed the greatest decline. Until recently the death rate from tuberculous peritonitis frequently reached 7 and 8 per 100,000, whereas in the last couple of years it has gone down to 1 per 100,000. The causes of these declines are attributed to the measures that the health authorities have adopted. The first is the complete pasteurization of milk, except the certified, and the second is the annual examination of almost 100,000 food handlers, as the belief is that the greatest part of the transmission is by means of contaminated food supplies.

The Diagnosis of Tuberculosis in Childhood.—SMITH (*Atlantic Med. Jour.*, 1925, 28, 725) states that the most common and most positive finding in children who have positive tuberculin reactions is the presence of small rounded shadows outside of the hilus. These have been shown by autopsy to be small tuberculous foci in the lung or along the bronchi. They may be very faint if the tubercles are young, denser if fibrosed and very dense if calcified. They may be very few just outside of the hilus, or may be scattered throughout the lung in small numbers, or may be numerous. These small mottled shadows are not seen when the tuberculin reaction is negative. They are nearly always present when the tracheal whisper is transmitted lower than the fourth dorsal spine. It is not claimed that the presence of these small foci is responsible for the increased whisper transmission, but they are probably like sentinels, showing that there are greater changes in the mediastinum due to lymph nodes or lung involvement. Pleural thickenings, especially interlobar plastic pleurisy or effusions, always suggest tuberculosis. Infiltrations of the lung tissue with many small or large shadows are seen in disseminated or bronchopneumonic tuberculosis and in general miliary tuberculosis. The lung involvement often starts from the hilus region. A true caseous pneumonia casts an even shadow, involving a part of or all of a lobe. It rarely has the distribution of a lobar pneumonia. Fibrosis, cavitation and all of the later changes are seen in older children. From these statements it is evident that in a child tuberculosis in the bronchial nodes is the most frequent lesion found, and is at the same time very easily overlooked. Like many other obscure conditions in medicine, one has to think of its presence in order to make the diagnosis. When a child is seen who is pale and droopy, distinctly undernourished, or with a history of loss of weight, with bright eyes, long lashes and hairy arms and nape, tuberculosis should be suspected. A positive tuberculin test will show that the child harbors the bacillus. Then a temperature record should be kept to see if there is activity of the process. A careful physical examination, with special attention to the intrascapular region, will

often show a tracheal whisper to the fifth or sixth dorsal spine, and occasionally an asymmetrical upper line of pulmonary resonance. The lungs should also be examined with great care, especially in the nipple region and axilla, for persistent dry rales here are suggestive, as are signs of dry pleurisy or effusion. The superficial nodes must all be palpated, and the abdomen carefully searched for masses or ascites. The spine and bones must be carefully examined. Signs of early meningitis, such as crossness, headache and vomiting, must not be forgotten. The roentgen-ray plate may show definite lesions, but even when it is quite normal we are justified in localizing the disease in the bronchial nodes in the absence of other definite findings. The only signs may be a positive skin test, the aspect of the child, a failure to gain weight, a slight irregular fever, a lowered transmission of tracheal whisper and a few small dense shadows outside of the hilus. This makes a symptom complex which is definite enough, once the evidence is all put together. Such children need care, and need it at once, before the trouble extends to vital organs. They do wonderfully under a proper regime, but may do badly if neglected. A few weeks or months of rest cure, with sun, air and proper food, will often bring the temperature down to normal, start a rapid gain in weight and change the entire appearance of the child, as well as its future progress. Still it is a sad fact that many such children are up and about, driven to school or to play, when the evidence is quite plain on their faces to one with seeing eyes. The hope of stamping out this plague lies in attacking it here in its truly incipient stage, while the results are apt to be good, instead of waiting for the serious and almost hopeless later stages to develop. All physicians should learn to be on the alert for these early curable cases.

Vaccine and Serum Treatment in Bronchopneumonia of Children.—DUFOURT (*Presse méd.*, 1925, 33, 829) studied 100 cases of bronchopneumonia, and he showed that the disease is usually caused by the pneumococcus, enterococcus and sometimes by both. The streptococcus was found in 1 or 2 out of 10 cases, and almost was in secondary bronchopneumonia. He used a vaccine containing the pneumococcus, enterococcus, staphylococcus and the tetragenus. The vaccine was used alone in 80 per cent of all the cases. A dose of 0.25 or 0.5 cc. was injected on the first day in infants and young children. On the second day 0.33 or 0.5 cc was given and on the third day 0.5 to 1 cc. were given. Daily injections of 1 cc. were continued until fever and grave functional signs subsided. In older children and in adults a double dose was given. An improvement of local and general phenomena occurred after three or four injections. If five or six vaccine injections failed then antistreptococcic serum was tried in a dose of 30 cc. in infants and 60 cc. in children. In bronchopneumonia caused by streptococci improvement under the serum appeared on the third day. The injection of the serum was continued daily until definite disappearance of the infection.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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Intravenous Bromid Therapy in Eczema.—Lebedjew had reported in 1924 the beneficial effect observed in the treatment of acute vesicular eczema, especially when a neurotic factor was involved through the intravenous injection of sodium bromid. Since the original report several additional favorable reports have appeared, including the present one by HUBSCHMANN (*Dermatol. Wchnschr.*, 1925, 80, 828). The method seems to be effective in proportion to the acuteness of the process. Itching and oozing may disappear from an acute extensive eczema almost overnight. In the more chronic cases relief is slower, but the majority of patients are helped. Chronic eczema shows the least response. The drug is injected intravenously in doses of 10 cc. of a 10 per cent solution of sodium bromid in physiologic salt solution. Initial doses of 3 to 5 cc. may be given but are rarely necessary. Two to five injections are often sufficient, but as high as fifteen may be necessary to give relief.

Chronic Erythema of the Legs in Young Women Due to Thin Stockings.—WEBER (*Brit. Jour. Dermatol. and Syph.*, 1925, 37, 259) discusses in a very interesting fashion the recent contributions to the literature and his own observations on a chronic erythema of the leg in the region of the ankle, occurring in young girls and associated with sclerodermatous thickening and nonpitting elephantiasic changes in the affected skin. While the condition at its outset suggests to some extent erythema induratum of Bazin, all observers are agreed that apart from a hypostatic background, it has no connection with the tuberculous condition. Apparently there is a permanent atony of the superficial blood capillaries. In some cases there seems to be an association of chilblain-like lesions. MacCormac, Dore and the author himself feel satisfied that the wearing of thin silk stockings and short skirts in cold weather is the exciting cause acting upon a predisposing skin and vascular background.

Treatment of Skin Sensitization to Sunlight by Peptone Injections.—CASTLE (*Brit. Jour. Dermatol. and Syph.*, 1925, 37, 267) reports a case of an elderly man, who for fifteen years had suffered from extreme irritability of the skin on exposure to sunlight. Four injections of Martindale's peptone and a quinin cream apparently produced a com-

plete cure. The fourth injection was followed by a fairly severe reaction but without unfavorable effect. The patient was able to return to South Africa, from which country he had been an exile on account of his condition.

Purpura Hemorrhagica and the Treatment of Syphilis.—Very few reports of the complication of arsphenamin treatment, long known in Europe as aleukemia hemorrhagica, have appeared in American literature. The condition is apparently an unfamiliar one. Inasmuch as it is a grave complication of neoarsphenamin and sulpharsphenamin treatment, it deserves greater notice. O'LEARY and CONNER (*Am. Jour. Syph.*, 1925, 9, 262) report 2 cases following the administration of sulpharsphenamin, in both of which they were able to ascertain that the rapid destruction of blood platelets and the lengthening of the bleeding time were the two most striking features. The leukopenia which has formerly been regarded as connecting the condition with aplastic anemia did not occur in one of their cases and was not extremely pronounced in the other. There was moreover some increase in the large mononuclear count. The first patient apparently recovered as a result of subcutaneous injection of 1 cc. of fibrogen. The second patient received 1 cc. of a 3 per cent solution of coagulen ciba subcutaneously and 0.75 gm. of sodium thiosulphate intravenously. The authors feel that hematopoietic crises may have been responsible instead of medication for both recoveries. The bleeding times and platelet counts were not markedly affected by this treatment. It is interesting to note that LASERSOHN (*Jour. Am. Med. Assn.*, 1925, 85, 436) reports a case of so-called "hemorrhagic encephalitis" following sulpharsphenamin injection, in which the clinical picture of multiple cutaneous hemorrhages with hemorrhage into the subdural space and blood in the spinal fluid is much more suggestive of a syndrome of postarsphenamin hemorrhagic purpura with coincident cerebral hemorrhage than it is of the typical hemorrhagic encephalitis. This case was treated with sodium thiosulphate without result.

Nonspecificity of the Luetin Test.—SMITH and GILL (*Am. Jour. Syph.*, 1925, 9, 292), using a commercial preparation, found that the luetin tests with the material which they employed were completely nonspecific and unreliable in diagnosis.

Sensitization to Adhesive Plaster.—BROWN (*Arch. Dermatol. and Syph.*, 1925, 12, 69) reports a second case in the literature of specific sensitivity to a particular adhesive plaster. No effort was made to investigate the element in the composition of the adhesive plaster responsible for the sharply defined local dermatitis which it produced, but the fact that the particular brand of adhesive plaster was responsible was apparently established beyond discussion.

Etiologic Factors in Erythematous Lupus.—THRONE (*Arch. Dermatol. and Syph.*, 1925, 12, 33) studied 38 cases, reaching the conclusion that in early cases of the discoid type removal of focal infections before atrophy sets in, together with simple local treatment, is apparently curative. Removal of focal infections seems to prevent recurrences.

Vaccine treatment (using a hemolytic streptococcus vaccine) was of no value. No evidence of a tuberculous factor in the condition could be discovered. On the contrary, a tuberculous cause in discoid erythematous lupus seemed to the author to be eliminated.

Influence of Potassium Iodid on Experimental Syphilis in the Rabbit.—PEARCE (*Arch. Dermatol. and Syph.*, 1925, 12, 1) apparently demonstrated that the regular administration of small bi-weekly or weekly doses of potassium iodid to rabbits (0.006 and 0.0003 gm. per kilogram) modified the severity and shortened the duration of the experimental disease as measured both by the character of the primary orchitis and the general manifestations. The disease which developed in the rabbits treated with iodid resembles in many ways that of normal rabbits of relatively high resistance in which few or no secondary lesions arise. It is suggested that the therapeutic action of potassium iodid in experimental syphilis of the rabbit is associated with the stimulation or reinforcement of the host's resistance mechanism.

The Wassermann Test, with Special Reference to Sulpharsphenamin.—BELDING (*Arch. Dermatol. and Syph.*, 1925, 11, 736) finds that prolonged treatment with the arsphenamins may not give as favorable serologic results as varied or mixed treatment. From his cases it appeared that sulpharsphenamin does not offer a sufficient difference from other arsphenamins to make it a valuable aid in treating arsphenamin-fast patients with fixed positive Wassermann reactions.

GYNECOLOGY

UNDER THE CHARGE OF

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Actinotherapy of Genital Tuberculosis.—According to SCHMITZ (*Radiology*, 1925, 4, 283), actinic therapy is rapidly gaining in importance in the treatment of surgical tuberculosis, and therefore a report of his observations on the treatment of tuberculosis of the female genitourinary organs with ultraviolet light and roentgen rays may be of practical value. The technic employed in his clinic consists in the daily application of a light bath of an hour's duration from an Edison carbon light diffused by a reflector. The anterior and posterior body surfaces are each exposed for one-half hour. This is followed by the application of the ultraviolet light obtained from an air-cooled quartz light, according to Rollier's method. The head is always covered and the body is divided into five parts. The exposures begin with one

minute anteriorly and posteriorly on the first day, and are gradually lengthened until exposures of fifteen minutes are used daily over anterior and posterior surfaces. With this method erythema is never seen, but a pronounced tanning of the skin is produced. The treatment is given every other day as soon as the local findings begin to improve and twice a week for an entire year when local healing has been attained. If a rise in temperature should occur the treatment is interrupted until the patient has been afebrile for ten days. If the tuberculous exudate or infiltrate does not begin to decrease within four to six weeks roentgenotherapy is added to the violet-ray treatment. The roentgen rays are applied locally, and they must be hard and filtered to produce a homogeneous penetration of the entire diseased area. The dose must be small and should be from 10 to 5 per cent of a full skin dose attained at the depth of the disease. The 5 per cent dose may be repeated every three weeks, and the 10 per cent dose every six weeks until resolution of the tuberculous process is complete, which occurs ordinarily within four to six months. If after the second roentgen-ray treatment the general and local condition has not markedly improved then the case may be considered refractory to actinic therapy. The roentgen rays may also cause a temporary amenorrhea, which is desirable. Actinic therapy does not interfere with surgical procedures that might be indicated as the evacuation of abscesses or the removal of ascitic fluid through a celiotomy. The ascitic fluid should always be removed if it has been present longer than four weeks. There must also be no neglect of the general management, as absolute rest in bed, open air, sunshine, wholesome nourishing food and medication.

Roentgenotherapy of Uterine Cancer. — A report from Leningrad, based on 421 cases treated by radium between the years 1914 and 1921, has been presented by POLUBINSKY (*Zentralbl. f. Gynäk.*, 1925, 49, 1193). Of this group there were 309 cases of primary carcinoma of the uterus, 13 cases of malignant disease of other organs, 4 benign tumors of the uterus, 39 recurrences after radical operation for uterine cancer and 56 cases in which prophylactic irradiation was given after removal of the uterus. In this clinic 25 to 30 mg. of radium element is used for twenty-four hours, repeated every three to four days until ten to thirteen treatments are given, or a total dosage of from 7000 to 8000 mg. hours. The mortality of the series was 4 per cent, chiefly from sepsis, while complications, such as inflammatory exudate, pus collections and hemorrhage occurred in 7.8 per cent and fistulas occurred in 9 per cent of the cases. Satisfactory primary results were obtained in 91 per cent of the cases, while an average of 20 per cent of all cases showed a good late result. In general the recurrent cases reacted poorly to irradiation. In the cases that were irradiated after radical operation there was only a 2 per cent mortality, and there were only 14 per cent of recurrences. The end results were poor in the cases of cancer of the vagina, vulva, ovary and rectum. As a result of ten years' experience the author believes that in cervical cancer radium gives just as good results as operation and without mortality nearly as great. This is especially noted in cases where the cancer has already begun to pass into the borderline stage of operability. If the cases have been subjected to radical operation it is always advisable to

give prophylactic irradiation. It should be remembered that the application of radium is dangerous and of no value in cases that are cachectic, in the presence of metastatic tumors, in cases where the tumor is adherent to the pelvic bones and in the presence of fistula. The results of radium irradiation are dependent upon the age of the patient (worse in young women), the extent of the disease, the histologic structure of the tumor (the results are poorer in cylindrical-cell carcinoma than in flat cell growths) and on the size of the dose.

Ovarian Dermoids.—As the result of his analytical study of the histories of 100 consecutive patients with ovarian dermoids who were treated in the Mayo Clinic, KOUCKY (*Ann. Surg.*, 1925, 81, 821) states that the presence of the ovarian dermoid is not markedly inimical to conception and childbearing. In this series 20 women had never been married. Sixty (75 per cent) of the 80 married patients had borne a total of 184 children. Three of the remaining 20 patients had had miscarriages, leaving 17 of the married women who had never been pregnant. Of these, 3 had been married two years or less, 9 had large uterine fibromata, while in 5 the dermoid cyst was the only gross pathologic condition and may have been a cause of the sterility. Forty-two patients came to the Clinic with no complaint referable to the dermoid. Twenty-seven of the 58 patients who had symptoms apparently due to the dermoid complained of pain or a bearing-down sensation. Seventeen patients came to the clinic because of a tumor which they could feel in the lower abdomen. Attacks of acute pelvic pain were the only symptoms in 5 cases. A fistula from the vagina to the dermoid was present in 2 cases. Three tumors in this series had twisted pedicles and 2 were completely twisted off. One had implanted itself on the posterior wall of the uterus, and the other on the greater omentum; this tumor could be manipulated into the upper abdomen. In the 3 cases the torsion was chronic. Although one or two complete twists were present in all, complete loss of circulation had not resulted. In the entire series infection occurred in 3 cases. In 1 the tumors were bilateral, and both were infected. One of the other 2 was associated with a tuboövarian abscess on the same side and the other was apparently induced by a twist of the pedicle. Other types of ovarian cysts were associated with the dermoids in 17 patients. In 1 case bilateral simple cysts were present; in 4 cases simple cysts were present in the same ovary and in 8 cases simple cysts were present in the other ovary. Associated bilateral chocolate cysts were present in 1 case. A multilocular cystadenoma was in the same ovary as the dermoid in 3 cases. There was 1 case of malignant degeneration, this being a squamous-cell cancer in a woman, aged forty-eight years. Thirty-nine of the cysts in this series contained teeth, the number varying from one to twenty-eight, two or three usually being found. In most cases the teeth were buried under the skin and fibrous tissue of the *focus*, which is the name applied to the parenchymal portion of the cyst which projects into its cavity. When bone was present the teeth were usually imbedded in it, and in this series bone was present in thirty-three cysts. In only 2 cases did the bony mass superficially resemble a normal bone, a jawbone in both cases. Microscopically, squamous epithelium was found in all cases. The typical dermoid squamous epithelium resem-

bled that found in the mouth. Hair was present in all but 1 case. Typically the hair was from 10 to 15 cm. long, reddish-brown and loose, tangled or even felted. Much of it was frequently implanted at both ends, that is, growing from one end and into the opposite wall at the other. Sweat glands, closely resembling the normal sweat glands, were present in 80 cases. Tissues derived from the mesoderm were present in 94 cases, as evidenced by fat, areolar tissue, muscle, bone, cartilage and certain parts of the teeth, as the dentin. Derivatives of the entoderm were demonstrable in fifty-seven dermoids. In eight specimens an intestinal type of mucosa was found. This consisted of a single layer of columnar cells with definite crypts. In two, glands not unlike Brunner's glands were present. These gastro-intestinal structures had a thick, smooth muscle wall indefinitely arranged in two layers.

OTO-RHINO-LARYNGOLOGY

• UNDER THE CHARGE OF

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The Use of Strychnine for Disturbances of Balance, in Subjective Sounds in the Ears and in Defective Hearing.—BECK (*Ztschr. f. Hals Nasen u. Ohrenh.*, 1924, 9, 222) has experienced very beneficial results by giving strychnin in cases of subjective vertigo, tinnitus aurium and objective derangements of equilibrium. Auditory acuity was improved in 2 instances. The favorable action was thought to be due to an increased sensitiveness to stimuli from the sense organs produced by the drug. Those conditions due to vasomotor disturbances responded especially well to the strychnin therapy, so that one might expect satisfactory results in cases of cerebral vertigo associated with such vascular diseases as arteriosclerosis. The initial dose was 1 to 2 mg. daily, increasing by 1 mg. up to 6 mg. daily, and then decreasing the dose to 1 mg.

Contributions to the Study of the Sphenopalatine Ganglion.—"The sphenopalatine ganglion is the second largest nerve center in the head and the largest nerve center outside the cranial cavity. As such, it assumes a position of greatest importance to the nose and throat specialist. It innervates and is intimately connected with practically every region treated by the otorhinolaryngologist. Its distribution is so extensive as to give symptoms directly and reflexly to practically every part of the body. It involves most of the cranial nerves, the cranial and visceral autonomic system and some of the spinal nerves, with remote effects produced through parts not yet traced." Recognizing the consummate importance of this structure, RUSKIN (*Laryngoscope*, 1925, 35, 87) describes its systemic, regional and topographic anatomical

relationships in detail, and describes a method of injecting the ganglion through the roof of the mouth by way of the posterior palatine canal. Employing a 22-gauge platinum needle, 45 mm. long, mounted on a syringe at about a 45-degree angle, with the patient in the lying position and head extended, the author locates the posterior palatine foramen by palpating the edge of the hard palate and inserting the needle 5 mm. anteriorly and about 0.75 cm. medial to the second molar tooth. The needle is then inserted through the canal to a depth of 3.5 to 4 cm. For anesthesia 1 per cent novocain with adrenalin is used. For alcoholic injection the posterior palatine canal is first located with novocain, then followed with alcohol. The following conditions have yielded to the treatment: External cricoidynia; lower jaw toothache; glossodynia; earache in case of Eustachian tube and middle-ear lesions, as well as secondary to cancer of larynx; pain of laryngeal tuberculosis and herpes of the shoulder; relief of spasm of the esophagus; relief of spasm of face and upper respiratory tract; all syphilitic headaches; malarial headache; ophthalmic migraine; dysmenorrhea; lumbago; intercostal pain (neuralgia); gastric pain; nausea and diarrhea; myalgias of neck muscles; sciatica; maxillary neuralgia; tic douloureux; sensory facial neuralgia; pain in upper teeth and sensation as though teeth were too long; feeling of foreign body in throat; persistent itching of external canal; herpes zoster oticus and taste disturbances. In addition, the author has found it valuable in producing anesthesia for tonsillectomy, radical antrum operations and for certain operations having to do with radical ethmoid, sphenoid and septal surgery. The author, concluding, considers sphenopalatine ganglion neuralgia as a combination of four syndromes: (1) Sensory facial (seventh nerve) syndrome; (2) maxillary (fifth nerve) syndrome; (3) sympathetic syndrome; (4) sphenopalatine ganglion-cell syndrome—all of which may occur singly or in combination.

Report of the Committee on the Problems of the Hard-of-Hearing, Section on Laryngology, Otology and Rhinology.—A committee, including HAYS, NEWHART, PIERCE, PHILLIPS and SHAMBAUGH (*Jour. Am. Med. Assn.*, 1924, 83, 2094) constituted to investigate the problems of the hard of hearing, reported the following ideas on the subject, as gleaned from 150 replies to a questionnaire sent to 1000 members: “(1) The most important etiologic factors producing deafness are nose and throat conditions that directly affect the Eustachian tube. (2) Deafness is decreasing because more attention is being paid to nose and throat conditions in childhood. (3) Otosclerosis is comparatively rare; nerve deafness is rare except in syphilis and meningitis. (4) Roentgenotherapy is absolutely without value, except so far as it affects the lymphatic tissue in the nasopharynx; mechanotherapeutics or electrotherapeutics produce no beneficial results, although some forms of vibration are of temporary benefit. (5) Ethical specialists urge deaf patients to wear suitable hearing devices, to stay away from quacks and to learn lip reading.”

Lung Abscess following Tonsillectomy.—“A great deal of reflection and study has been devoted to the subject of lung abscess following tonsillectomy. At the present time there are two main theories of its

origin. One is that the lung suppuration is usually due to the aspiration of adenoid or tonsil tissue, or of potentially infective blood and mucus, or the crypt content or any combination of these. The other is that a septic embolus becomes dislodged from one of the thrombosed vessels in the operative area, and finally settles in the lung where an abscess is initiated." After reciting the opinions of several surgeons, answering this questionnaire, MYERSON (*Arch. Otolaryngol.*, 1925, 1, 137) gives the results of recent bronchoscopic studies of tonsillectomy under general anesthesia, in which 155 of 200 patients showed the presence of the tonsillectomy blood mixture in the bronchi, without a single pulmonary complication. From this the author concludes: "That the cause of these complications does not lie in the aspiration of the tonsillectomy pharyngeal content into the bronchial tree, or the factors that influence this aspiration, but rather in the failure of the evacuation of this potentially infective material and the factors that influence this failure of evacuation and expulsion from the bronchial tree and lung bed"—such factors as the cilia of the bronchial mucosa and the elasticity and compressibility of the lung tissue. Any condition, such as increased concentration and prolonged administration of ether, influenza, pneumonia or tuberculosis, which damages the pulmonary and bronchial elements, would indicate an inability to expel the aspirated material, predisposing to a site of election for a suppurative lesion. From his studies, the author admonishes that all tonsillectomy patients should be given a careful preoperative survey, with special reference to the pulmonary tract, so that "in the presence of known pulmonary disease we should be forewarned and plan our operative procedure accordingly."

The Comparative Value of Transillumination and Roentgenography in Diagnosis of Maxillary Sinus Disease (Author's Methods).—As the maxillary sinus is the most constant of all the nasal accessory sinuses, BRIGGS (*Ann. Otol., Rhinol. and Laryngol.*, 1925, 34, 485) describes, in detail, its anatomic features. After a comprehensive review of the literature having to do with the various opinions as to the relative merits of transillumination and roentgen-ray examination of the maxillary sinus, the author describes his methods of examination. In transillumination, with the patient seated on a high stool in a very dark room, with head tilted backward, mouth open, lids closed and eyes directed downward, the 6-volt lamp, controlled by a rheostat and placed on a shank having two 45-degree angles, and so constructed as to prevent the escape of light, is placed against the lower eyelid directly below the pupil, pressed backward beyond the infraorbital ridge and directed downward toward the floor of the antrum. If not obstructed the light will illuminate the floor of the antrum and can be observed as a pink area on that part of the roof of the mouth near the molars and the buccal wall above the alveolar process. For roentgen-ray films he prefers the chin-nose position, as having the advantage of bringing the antrum nearer the plate, making a less acute angle with the central rays and, consequently, insuring less distortion. The author believes that both roentgenography and transillumination are of the greatest value in diagnosing pathologic conditions of the maxillary and frontal sinuses. The roentgen ray is superior to transillumination in outlin-

ing the anatomic relations, showing foreign bodies, as unerupted teeth, and perhaps in detailing shadows of chronic thickening of mucous membrane and bony walls. Transillumination is more reliable in acute infections and is more sensitive to the retained antral secretions. The author states that were he limited to the use of only one of these exceedingly valuable methods of examination, he would choose transillumination.

Recognition of Sinus Disease in Children.—"The work of Dean and Byfield has stimulated investigation for the relief of sinusitis in children, and has resulted in untold benefits for children suffering from 'chronic colds' due to infection of the paranasal sinuses." Although our attitude in regard to sinusitis in children is easily explained when we recall that it has never been impressed upon us that children possess sinuses prior to puberty, BARLOW (*Ann. Otol., Rhinol. and Laryngol.*, 1925, 34, 378) emphasizes the fact that the maxillary sinus appears in the third month of fetal life and at twelve months of post-fetal life is quite well developed; that the ethmoid cells are present in the latter part of the third and fourth fetal months, and that the frontal sinus may be found in the third or fourth month of fetal life, but is usually recognized only after the third or fourth year of postfetal life. He believes that an acute suppurative sinusitis in children rarely returns to normal or that the infection entirely subsides, so that a low-grade residual infection of the mucous membrane lining continues and there remains a mild type of chronic suppurative sinusitis. The most prominent manifestation of chronic sinusitis is a mucopurulent discharge from the nose—a discharge which is quite profuse, associated with a vestibulitis and frequently with excoriation of the nares. The value of roentgen ray in the diagnosis of these conditions is stressed. From the therapeutic standpoint, in the chronic forms, the author offers surgical procedures as the most effective—draining the antrum and opening the anterior ethmoids.

Direct Blood-stream Infection through the Tonsils.—Having previously shown (*Arch. Int. Med.*, 1924, 33, 473) by photographs of microscopic sections that the epithelium lining the tonsillar crypt is more vascular than that covering the surface of the tonsil, and that the common pathologic lesion in chronic tonsillitis is a destruction of this epithelial lining, TANAKA and CROWE (*Arch. Otolaryngol.*, 1925, 1, 510) continued the study, calling attention to the anatomic arrangement of the capillaries in the epithelium and to the large veins that lie just under the epithelium that lines the crypts in the tonsil, and to suggest that the joint lesions and other general disturbances secondary to a chronic tonsillitis may be due to bacteriemia. The bulk of the context is composed of the explanations of composite drawings of tonsils injected with India ink and photomicrographs of the tonsillar sections in selected cases. After a brief, though comprehensive, clinical résumé of focal infections of the tonsil, the authors conclude that: (1) The epithelium that lines the crypt in a normal tonsil has a rich capillary blood supply; the large collecting veins that surround each crypt lie just under the basement membrane; (2) a destruction of this epithelium, in whole or in part, is the most common microscopic finding in chronic

tonsillitis; often the lining epithelium is replaced with scar tissue and occasionally definite ulcers are found. In either instance large numbers of bloodvessels have been thrombosed and they afford a pathway for the entrance of bacteria into the blood stream.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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The Etiology of Acute Appendicitis.—One hundred appendices diagnosed clinically as acute, removed by the surgical staff of the Boston City Hospital, have been studied bacteriologically and histologically by WARREN (*Am. Jour. Path.*, 1925, 1, 2). Of these 66 were diagnosed histologically as acute, 4 as acute periappendicitis, 15 as healing appendicitis and 1 as a healed appendix with obliteration of the lumen. The method of examination was as follows: The surgeon dropped the appendix into a sterile Petri dish which was carried to the laboratory. Cultures were taken, with aseptic precautions, from the wall of the appendix and from the lumen. The appendix was then fixed *in toto* in Zenker's fluid and sections made from the same areas as those from which the cultures were taken. The bacteriologic findings in the 66 acutely inflamed appendices showed *Bacillus coli* to be the organism most frequently encountered, being found alone in 25 cases and combined with other organisms in 12. *Streptococcus* occurred alone in 6 and combined with *Bacillus coli* in 9. *Bacillus proteus vulgaris* and *Bacillus pyocyaneus* were each found five times. There was a scattering of other organisms. The 4 cases of acute periappendicitis all occurred in females. Of these 2 showed pneumococcus Type I, 1 *Streptococcus viridans* and 1 gonococcus. Of the 16 healing appendices 1 showed *Bacillus coli* and 1 showed *Streptococcus viridans*. The remainder showed no growth. All early lesions were found at the margin of the lumen, and the inflammatory reaction was similar throughout the series irrespective of the organism found. Possibly streptococcal cases were slightly more hemorrhagic. The evidence brought by the study is against the hematogenous origin of acute appendicitis.

The Origin of Adenomatous Goiter.—KLINE (*Am. Jour. Path.*, 1925, 1, 2) reports the microscopic study of over 600 adenomatous goiters at Lakeside Hospital. At present there are two views concerning the origin of this condition, that of Beck, Woelfler, Ribbert and others who believe that it arises from multiple embryonal cell nests scattered through the tissue, which begin to enlarge from puberty onward; and

that of Virchow, Hitzig, Michaud, who contend that the nodules develop from adult thyroid tissues. As a result of the study the author inclines to the latter view. In his work he observed adult thyroid tissue apparently passing from its normal lobulation, by gradual changes, to circumscribed, encapsulated nodules histologically indistinguishable from adenomata. In sections of thyroid gland showing varying degrees of hypertrophy and hyperplasia more or less circumscribed areas are not infrequently found in which the hyperplasia is more marked than generally throughout the gland. The repeated changes in such glands to the colloid state apparently brings about in some an increase in stroma around and within the lobules causing greater circumscription of lobules than normal, or division of lobules into smaller circumscribed units. When hyperplasia occurs in these areas they gradually increase in size and become spherical in form. The capsule may be gradually acquired in one of two ways: (1) The compression of regional thyroid tissue with atrophy and replacement fibrosis thereof; (2) when the growing lobule returns to its colloid state, the older central acini usually take up more colloid than those in the periphery, which are younger. The pressure exerted toward the periphery results in atrophy and replacement fibrosis. The paper is well illustrated with plates.

Pathogenicity of Clostridium Botulinum.—An elaborate study of the conditions of toxin production of *Clostridium botulinum* which shows evidence of great thoroughness, skill and patience, is reported by STARIN and DACK (*Jour. Infect. Dis.*, 1925, 36, 383). The principal strain used was one designated as M7a², a single-cell isolation, highly toxic, recovered from the Greensburg, Pa., outbreak in 1921. Casein-digest-veal-infusion broth was used as a medium and cultures were incubated three to four weeks. Elaborate aseptic precautions were used throughout the work, controls rigidly observed and all doubtful results indicated. Rabbits were injected with spores of *Clostridium botulinum* intravenously and intraperitoneally. Detoxified spores were fed orally to rabbits, and detoxified spores were introduced into guinea pigs intraperitoneally, intravenously, intramuscularly and orally. Detoxified spores were injected into mice in all series as controls. White rats were used in one series and were found to be markedly resistant to the action of *Clostridium botulinum* toxin. The influence of calcium chlorid and quinin on the pathogenicity of the spores was investigated on account of their influence on the pathogenicity of the spores of *Clostridium tetani*. No influence was noted that could not be attributed to the action of the calcium chlorid or quinin alone on the animal organism. There was no agreement between the findings in *Clostridium botulinum* and *Clostridium tetani*. Collodion sacs containing spores of *Clostridium botulinum* were introduced into the peritoneal cavities of rabbits and guinea pigs. Paraffined sacs containing sterile toxin or toxin-freed cells were also used. This part of the work presented many difficulties. Evidence was obtained of the multiplication and toxin production of the organism in the body of animals, but the exact relationship between the organisms in the sac and the host was not found. Among the constant changes found in animals dying of botulism not hitherto reported they found marked stasis of the

contents of the gall bladder, urinary bladder and stomach. Marked icterus was noted in rats. Congestion of the stomach-wall was observed particularly in the stomach region, leading in some cases to definite necrosis. They conclude that detoxified spores can multiply in the animal and produce sufficient toxin to induce experimental botulism, but that the number of spores necessary to do this is quite large. The spores may remain latent in the animal body for at least as long as four months. *Clostridium botulinum* was recovered from widespread parts of the body after death from botulism, the highest percentage of positive results being recorded in liver, kidneys, spleen and cecum. Organs from such animals, macerated in salt solution, showed no evidence of botulism toxin. Antibody formation agglutinins in animals could be demonstrated.

Pneumonia Associated with *Bacillus Abortus* (Bang) in Fetuses and Newborn Calves.—A pneumonic condition in fetuses and newborn calves due to *Bacillus abortus* is pointed out for the first time by SMITH (*Jour. Exper. Med.*, 1925, 41, 639). The fetuses examined are placed in three classes: Those which have not breathed, those expelled with partly inflated lungs and a number of calves killed during the first week of life which were slightly premature. A detailed description of the lungs and their pneumonic areas is given. *Bacillus abortus* was demonstrated in all cases. The character of the pathological process, its extent and its bearing on the epidemiology of pneumonia is indicated.

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ORIGINAL ARTICLES.

THE BILIARY ASPECTS OF LIVER DISEASE.*

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WERE the project not a vain one, I would ask your indulgence to consider the state of our knowledge in case the biliary secretion, instead of the renal, was voided directly to the outside of the body. If, that is to say, the physicians of past times, whom we see in the Dutch pictures holding up a flask to the light, had had in that flask not urine, but bile. Knowledge would have been interestingly different. There would have accumulated a huge clinical pathology of the bile. For this secretion has its suppressions and its cholureses, its cylinders and desquamations, its pathologic albumin and other strange substances, as has the urine. But things are as they are; and until the specialist, with his little tubes, converts our inside into an outside, most doctors will have to be content with perceiving biliary disturbance at one or several removes.

Now, how small a biliary disturbance can the clinician perceive? Circumstances alter that case very much. The liver is the most silent of organs if only a moderate fraction of its cells are in a healthy state. The ducts from more than three-fourths of it can be abruptly obstructed, without causing even a ripple on the clinical surface of things.¹ Herringham² has collected a considerable number of cases in which, as a result of gradual obstruction of the left branch of the hepatic duct by a stone, the entire

* Read before the Association of American Physicians, May 5, 1925,
VOL. 170, NO. 5.—NOVEMBER, 1925

left lobe of the liver had atrophied. The patients in these cases never knew anything had happened to them. There was at no time any jaundice, and the condition was first recognized at autopsy. In such cases there had taken place, of course, a gradual compensatory hypertrophy of the portion of the hepatic tissue with unobstructed ducts. Liver cells have an astonishing ability to proliferate. After destruction of one-half of the hepatic tissue of dogs by chloroform, restoration may be complete within seven to nine days.³

The functional causes for biliary disturbance offer a far more complex problem than do mechanical ones. While the liver works extremely well, is a more than adequate mechanism, each cell being capable of doing at least four times the work in biliary excretion that it ordinarily performs, yet it is insensitive. It lets bile pigment slip past, never ridding the blood entirely thereof. It is, in fact, a threshold organ for this pigment, like the kidney; and there are natural and unnatural thresholds of bilirubin removal from the blood stream as in the renal instance. One may well believe that there is an unnaturally high threshold in congenital hemolytic jaundice and, perhaps, in pernicious anemia. During Frerich's time, sixty years ago, jaundice was frequently ascribed to functional causes that in the present day we would rule out of court. If a person had a fit of temper or another emotional shock he might turn up all yellow next day. With a more critical scrutiny of these cases they have disappeared. But one type of functional icterus, namely, that due to fasting, does remain. There can be no doubt that when the normal individual has been deprived of food for some hours bilirubin increases in his plasma. The state of affairs is subicteric, as in many other conditions. "Bilious" would be a better word, were it not in such bad repute.

You will note that by degrees I have come to talk of bilirubin and jaundice, not of biliary constituents generally. It is natural to think in terms of the bile pigment, for we know relatively little of the phenomena involving bile salts and cholesterol. Methods of quantitating these substances are difficult, and the results uncertain. Certain one can be, however, that the cholates play a far more important role, both normally and in disease, than does bilirubin, and that many more gall stones are formed out of cholesterol than out of bilirubinate. Bile salts are the substances responsible for most of the injury during biliary disturbances. They are, furthermore, a specific product of the hepatic parenchyma, whereas bilirubin is not. The amount of cholesterol in the bile can be greatly altered by the character of the food, as McMaster has proven definitely.⁴

It is customary to inquire, when one sees a case of jaundice, whether the coloration is obstructive or hemolytic in derivation. The distinction has clinical uses, though, of course, all jaundice

is blood derived. We now know, thanks to the work of Mann and his associates,⁵ that the formation of bilirubin from hemoglobin is almost, if not quite wholly, extrahepatic. But the liver hallmarks the pigment as it puts it out,⁶ with result that it can be recognized from that upon which the organ has not acted. There is a remarkably close relationship between current blood destruction and the intensity of a simple obstructive jaundice.⁷ Under normal circumstances the variations in the amount of hemoglobin circulating as blood from day to day find a direct, if not entirely accurate, expression in the amount of bilirubin discharged into the bile. The corpuscular wastage would seem to be recorded almost immediately in terms of bilirubin; the greater the number of cell deaths the more the bilirubin put out. When obstruction is produced, most of the bile pigment formed is retained within the body, and, other things being equal, the jaundice that ensues will be more intense when the animal is full blooded than when it is anemic. If it is bled the jaundice diminishes very nearly in proportion to the amount of hemoglobin withdrawn, only increasing again as the loss of blood pigment is repaired.

The intercurrent variations in hemoglobin and bilirubinemia during uncomplicated obstructive jaundice accord with each other so closely from day to day that it is evident bile pigment cannot be readily distributed to the tissues, else they would take up the slack, so to speak, of the bilirubin accumulation in the plasma, and there would be little diurnal variation therein. To test the state of affairs is an easy matter. On collecting a specimen of lymph from the leg of a long jaundiced animal, one finds that it contains a negligible quantity of bilirubin as compared with plasma procured at the same time. Evidently there exists a barrier to the passage of bilirubin from the blood. Tissue icterus is in point of fact only the imperfect, secondary, expression of a condition primarily confined to the blood pool. Its intensity is, however, conditioned to no small extent by the tissue state. Schürer⁸ and Jädasohn⁹ have recently described a singular condition which the former terms "icteric skin writing." In their cases urticaria occurred, or was induced by artificial means, in patients that were jaundiced. The urticarial wheals were far more deeply pigmented than the surrounding tissue. In some instances this was due merely to the accumulation in the wheals of lymph colored like that elsewhere. But in others more pigment had come through locally from the blood stream, and there was plainly an increased permeability of the vessel walls to bilirubin. The question is worth proposing whether an increased permeability of the vessels may not have a share in the development of fulminant icterus.

If jaundice is fathered by the blood then certainly it is born of the liver. In asking whether it is hemolytic or obstructive, one is really asking, does the blood break down so fast that the liver

gets clogged secondarily, or is the liver so clogged to begin with that the products of normal blood destruction can find no outlet?

Pathologic disturbances affecting the ability of the liver cells to excrete bile pigment are a frequent cause of jaundice. The book written by Brulé¹⁰ is instructive in this relation, and expresses well the French point of view as against that of a German school—the Germans are the metaphysicians of medicine—which would relegate all jaundice to mechanical causes. That there must be an icterus referable to cellular disturbances I believe most clinicians will agree. How else is one to explain dissociated jaundice, or the retention of two kinds of bilirubin, the so-called hemolytic and obstructive kinds? And how explain those cases in which, after operative drainage of the common duct, the bile, at first normal to all appearance, becomes lighter and lighter, though still copious, until finally a “white bile” is formed and the patient shortly dies with a greatly diseased liver?

It is simple to demonstrate the occurrence of jaundice from parenchymal disturbance by producing liver injury with chloroform.¹¹ As the injury develops the bile becomes progressively lighter and lighter, and shortly “white,” while at the same time jaundice puts in an appearance. The secretion is not glairy, of the sort that would cause obstruction, but watery and clear. There are no changes within the hepatic tissue, such as would cause obstruction. It is probable that the partial or complete rejection of bile pigment by functionally damaged hepatic cells will explain many of the recorded instances of anomalous van den Bergh reactions.

There is another pigment, urobilin, which is important in relation to biliary disturbances. It is not an essential constituent of the bile, but is derived secondarily from the bilirubin of the secretion, and is hence directly dependent upon it. As a recent writer has stated, clinicians believe urobilin (under which name urobilinogen may be included) to be formed in the intestines by the action of bacteria, resorbed in part from the gut, carried to the liver by the portal circulation, and, under normal circumstances, removed therefrom by this organ. The clinical belief is correct, as the recent work of McMaster and Elman clearly shows.¹²

Their experiments have proved that the history of the pigment is as follows: It is formed in the intestine from bilirubin by bacterial action, is resorbed in part, and ordinarily the resorbed portion is so completely taken out of the blood by the liver that only a trace reaches the urine. Of the portion taken by the liver some, perhaps all, is excreted into the bile, and hence the normal bile regularly contains urobilin. If, now, bile be diverted from the intestine so that no bilirubin reaches the gut, to be worked upon there by bacteria, the diverted bile soon comes to be free from urobilin; while if bile is prevented from reaching the intestine by ligation of the common duct urobilin soon disappears from both feces and

urine. No matter how greatly one damage the liver of the animal with obstructed common duct, or with a fistula through which the bile is lost, the excreta remain free from urobilin. The same holds true even when a large part of the blood is broken down within the body by experimental means.

The liver has not so large a margin of safety for urobilin as it has for bilirubin. If one tie off only a small twig of the hepatic duct some of the urobilin absorbed from the gut passes through the injured portion of the liver and is excreted into the urine. As result of relatively slight hepatic injury one has urobilinuria, whereas a much larger one would not result in bilirubinuria.

It would seem, from what has thus far been said, that urobilin might be relied on as a highly useful sign of liver injury. Unfortunately there is more to the story of it. We have been considering what happens under conditions when there is no infection. But when the liver is infected, things may be very different. If one obstruct the common duct after infecting the bile in the passages with urobilin-producing organisms, urobilinuria will occur.¹³ Many people have supposed that the liver cells themselves can form urobilin, but the evidence speaks conclusively against this. It is bacteria ensconced within infected ducts and perhaps within parenchyma, bacteria of a very special sort, which form the pigment out of bilirubin. To determine under what circumstances urobilin-producing organisms are found within the human liver will be an interesting task for the future.

Many of the bile constituents besides urobilin are resorbed in greater or less part from the intestine—bilirubin, cholesterol and, notably, the bile salts. The question may be asked, Is this resorption purposeful, brought about by a special arrangement? I do not believe that it is. Hinman¹⁴ has shown that when the ureters are introduced into the small intestine by operative means, with result that all the urine is discharged into the gut, the animal resorbs the urinary constituents so completely as to die of uremia. It is probable that a similar process, incident to the physiologic activities of the mucosa of the gut, will suffice to explain the passage back into the organism of the bile constituents. Whipple¹⁵ has trenchantly pointed out what would happen in case bile salts were quantitatively resorbed. With new salts being formed every day, and the old conserved through resorption, the patient would soon come to be, as he says, a pillar of bile salts. Granting all this, there can be no doubt that the body has adjusted itself to the resorption of biliary constituents so far as these influence its daily processes. Resorbed bile salts are known to stimulate bile secretion and for such reason are said to act as a "pace maker." In this relation it will not be amiss to point out that the bile obtained from a fistula animal is very different from the normal secretion. Owing to lack of the pace-maker influence the quantity secreted is greatly less than

normal. McMaster and Elman¹⁶ have recently intubated small ducts from the liver, while allowing the greater part of the bile to flow to the intestine, and they find that the secretion collected from day to day under such circumstances is about three times as copious as that one would get from the same liver portion if all of the bile were being diverted from the gut.

Biliary disturbances mean disturbances of other functions as well as of the biliary function itself. On prolonged obstruction bile salts cease to be formed. Some substances which should be taken up by the liver and excreted into the bile are no longer so excreted. The hepatic cells form those curious little bodies known as bile thrombi which are not, as many have thought, inspissated bile, but a mixture of lipoids and protein, a product of damaged cells. The hepatic tissue does not take up hemoglobin with anything like the normal avidity. It does not lay down glycogen as well, and the quantity of sugar in the blood is increased. It does not form hippuric acid as well on test. In all these functions the organ obviously suffers, and in many others of which we know little. Yet it carries on remarkably well. I am speaking now of cases in which there is frank obstruction. When, by contrast, the liver parenchyma is at fault recovery or death takes place within a short period usually. Those cases in which one sees a long-standing icterus, with an excretion of bile still going on into the intestine, are cases in which the liver has been forced to the wall by repeated, localized injury, so that there has come to be less hepatic tissue than will suffice for the excretion of the daily quota of biliary constituents. This sort of thing happens at a late stage in Laennec's cirrhosis.

Recently there has been a productive revival of interest in the bile. Until it began our conception of biliary matters had been a masterpiece of the antique. Workers since Quincke had merely dusted off this masterpiece. But now, within a few years, much has come to be known. Clinical attention has been aroused, however, not by the new learning, but by the development of methods for quantitating the amount of bile in the blood, for obtaining bile from the duodenum and by the attempts to induce the gall bladder to discharge its contents. The question arises whether, when these technical advances have been perfected, and their limitations defined, clinical interest in the bile will flag? I do not believe it will, for the reason that workers are beginning to test liver function successfully. Not a few of the tests advocated are carried out with substances which find their way into the bile. In using these substances it is essential to know whether one is measuring liver function generally or merely biliary function. Before the point is settled much will inevitably be determined of biliary problems, and that is fortunate, because the bile is not merely an excretion—it is a highly purposeful secretion, and one susceptible to further utilization as an indicator of the liver state.

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RHEUMATIC FEVER.*

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THREE diseases causing very great economic loss are tuberculosis, syphilis, and rheumatic fever. Not only are the early acute stages of these maladies time-consuming in a period of life when the victims are of greatest value to the community, but their late manifestations, a consequence of their inherent chronicity, cause many individuals to be so severely crippled that they are often less efficient productive units.

About the first two, many positive facts are known; they have clinical, histo-pathological, and immunological points of similarity. Even though their respective causative agents occupy different positions in the biological scale, some of their manifestations are similar allergic expressions. In both we know the etiological agent: In one of them, syphilis, even though much had been learned empirically concerning the effect of mercury and iodids in an era of purely clinical study, the discovery of the *Treponema pallidum* led to important development in specific therapeutics. In the other, although the tubercle bacillus has been known for many years, no

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striking specific therapeutic measures have been derived from this knowledge. The information at our disposal, on the other hand, has led to important measures in the prevention of the disease; also, to a knowledge of the natural history of the tuberculous infection. The etiology of rheumatic fever is still undecided, hence we are forced to compare it with infections the nature of which are better understood.

We shall, therefore, draw attention to several points of similarity between these three diseases. I am assuming that rheumatic fever is an infection, with a great variety of manifestations; some short in duration and apparently inflicting but little damage on the tissues of the patient; others having a chronic persistent course from the onset with marked evidence of deep-seated injury to the affected organs; and still others in which there are alternate periods of activity and latency.

In making these comparisons it is possible to imagine ourselves in a period where the etiological agent in all three diseases was unknown. At that time many conditions were confused with tuberculosis: phthisis, consumption, often included diseases not due to the tubercle bacillus, although in the majority of instances this was the offending microorganism. Even now, the differential diagnosis in certain patients may rest, not upon the determination of the presence of the tubercle, but rather upon discovery of some other causative factor.

In such an attitude must we often approach our patients with rheumatic fever. It is not possible to be absolutely dogmatic about many cases. Some have symptoms that help in classifying them quickly; about others we are less certain. Doubtless numerous conditions other than rheumatic fever have been and still are included under the term rheumatism. The recognition of many forms of bacterial arthritis has helped to narrow the field so that there is less confusion in differentiating the various diseases with inflammation of the joints as their chief features. The characteristic response of some manifestations of rheumatic fever to certain drugs, such as salicylates, is also a diagnostic aid, just as iodids were formerly used in the differential diagnosis of syphilis. These differential diagnostic methods, however, merely help in bringing certain conditions into a narrower nosological zone; they do not offer much assistance in pointing to the true nature of the disease.

For this purpose we must not only study the manifestations of rheumatic fever directly, but must compare them with other conditions of an apparently similar nature and apply the positive information we have concerning the latter to the malady less well understood. But in making these comparisons it is well to keep constantly in mind that the diseases under consideration are not parallel in all respects. It is in the point of divergence that the peculiar picture of disease is brought out so that each infection has

more or less specific characteristics by which it is recognized as a separate entity. Thus the clinical manifestations of an infection are often determined because of the organs or tissues in which the virus is localized and the specific pathological responses occur. For example, in tuberculosis the lung seems to be most often involved because of its peculiar anatomical structure, and also because of a position favoring implantation of the tubercle bacillus. Similarly, in rheumatic fever the connective tissues in close apposition to large endothelial-lined body cavities or to synovial membranes seem to be especially predisposed to involvement. Nevertheless, if phthisis or scrofula were the only tuberculous manifestations recognized by us we would miss many important features of tuberculosis, so in the consideration of only arthritis and endocarditis we obtain an incomplete picture of rheumatic fever.

In the discussion concerning the relation of heredity and environment to the etiology of tuberculosis, and in the consideration of its contagious nature, the long periods of latency were very confusing factors; it is now well understood that five or ten years may elapse between the time of obvious opportunity of acquiring the infection and the appearance of symptoms. As Opie⁹ remarks: "Tuberculosis has so few features of a contagious disease that its infectious nature was in dispute until Villemin's successful experimental inoculations and Koch's demonstration of the tubercle bacillus." It seems probable from clinical observation that similar periods of latency exist in cases of rheumatic fever and that comparable factors in heredity and environment play a role in the etiology of both diseases. For example, Cheedle¹ states that 70 per cent of his patients with rheumatic fever in private practice showed more than one case in the same family. Lately, St. Lawrence,¹² in a study of 100 families with rheumatic fever and 100 with tuberculosis in the St. Luke's Hospital Out-patient Department, showed that practically one-half the families in each group had 2 or more cases per family. There are also several important studies pointing to the possibility that house infections occur in rheumatic fever. It is, therefore, especially difficult to evaluate properly the relation of heredity, direct family infection, and house infection in the etiology of this disease. A recent report of Grenet⁶ upon five distinct epidemics of rheumatic fever among Italian troops suggests strongly that direct infection from one person to another may take place and strengthens the opinion that the disease is due to a specific etiological agent.

In studying the various types of manifestations in patients of different ages we are struck by the fact that in both tuberculosis and rheumatic fever severe general acute manifestations are more frequent in the young than in the old. In succeeding decades of life there is a transition from generalized manifestations to more localized lesions. This we know in tuberculosis to point to the

development of an immunity or rather an allergy to the infectious agent. Perhaps a better example of this general principle is seen in syphilis where during the early secondary period there is a widespread dissemination of the *Treponema pallidum* and a generalized macular eruption. With each relapse these manifestations tend to become more and more localized and each individual lesion to be more deep seated and nodular. We now recognize this development of allergy to be an effort on the part of the body to restrict the activity of the virus to smaller and smaller areas. In tuberculosis this allergy is manifested in adults by a greater frequency of chronic tuberculosis of the lung. In rheumatic fever a similar tendency may be seen in the development of more frequent and severe joint lesions in adults than in children, possibly by a tendency to development of chronic arthritis. It does not require a great stretch of the imagination to picture the progressive thickening of the heart valves, the development of the mitral stenosis, the progressive increase of an aortic insufficiency, as sequelæ of the development of an allergy similar to that seen in tuberculosis. Sclerosis, the development of firm connective tissue from an inflammatory base, is a well-recognized feature of later periods of both diseases.

Let us return for a moment to an earlier age period, namely, that of childhood. Involvement of the central nervous system is seen relatively more often in the young than in adults. In children, tuberculosis often manifests itself as a generalized miliary tuberculosis, not infrequently, as a tuberculous meningitis. Similarly, chorea is a common manifestation of generalized rheumatic fever in the young. Accompanying tuberculous meningitis in a child we expect to discover other foci of infection in the lung or perhaps in all the viscera; similarly, in the presence of chorea we are not surprised to find cardiac lesions and frequently wide-spread subcutaneous fibroid nodules. In tuberculosis the severe manifestations usually lead to death; in rheumatic fever, the type of infection, being less severe, leads to a chronic disease which most often expresses itself as a persistent carditis.

A variation in the susceptibility of various systems of the body at different ages has already been suggested. These systems need not necessarily all be simultaneously involved. In other words, if the virus be generally disseminated, all of the organs do not necessarily respond to this invasion at the same time. For example, although we usually see in children extensive evidence of involvement of the various structures, the child at one time may have chorea, a little later subcutaneous nodules, and still later evidence of marked cardiac disease. The order of involvement does not necessarily follow that given above. In fact, we have examples of nodules with cardiac symptoms, or nodules alone and later chorea. Only one type of manifestation may be detected for a long time; and this fact supports the conception that chorea or

subcutaneous nodules occurring in the absence of any other symptoms are really rheumatic in nature.

The tendency for a person to have several attacks of rheumatic fever has long been known. Two points of view regarding this phenomenon are possible; the first is that he is susceptible to the peculiar type of infection and that each attack is the result of reinfection in the same manner as we regard several attacks of lobar pneumonia in one individual as due to different types of pneumococci. The second conception is that the various acute attacks are evidences of relapses of an infection having alternate periods of latency and activity. This view predicates that the patient is infected but once and that clinical recovery is due to the development of a partial immunity resulting in an incomplete elimination of the infectious agent from the body; later some depressing influence lowers the patient's resistance and the dormant virus again becomes active. The well-known chronicity of rheumatic fever in children is good evidence of the capacity of the infectious agent to persist in the body; and it is not rare to encounter similar examples in adults.

All grades of transition between these very chronic cases and those showing rapid and apparently complete recovery without the intervention of drugs are seen. Not infrequently one meets patients with the signs of chronic infection in evidence for many months, in whom finally the inflammatory process seems to have come to an end; in other words, the patients even with marked cardiac disease have apparently overcome the infection. I use the word "apparently" because experience has taught us to assume the same attitude toward recovery as those responsible for the care of tuberculous patients take in using the term "arrested." In both instances the physician is prepared to see at any time a reawakening of activity.

Unfortunately the etiological agent of rheumatic fever has not been demonstrated conclusively; nor has it been possible to reproduce in animals the characteristic clinical or histo-pathological picture of this disease. This may be due to the absence of the causative agent in the material injected or to the failure of the lower animals to react in the same manner as man to the same irritating substance. Many consider the disease to be due to the so-called *Streptococcus rheumaticus*, which is really the nonhemolytic streptococcus; but I do not think this opinion can be unqualifiedly accepted. The endocardial vegetations and myocardial lesions so characteristic of the disease known as subacute bacterial endocarditis are also seen in animals properly inoculated with streptococcus viridans. The characteristic microscopic lesions of rheumatic fever, namely, Aschoff bodies are not found in the hearts of either these patients or animals. How then are we to regard the occasional recovery of nonhemolytic streptococci from the blood or gross lesions of patients with rheumatic fever? Up to the present we⁶ have been unable to

place the strains so recovered in any small number of biochemical or immunological classes such as has been done with the pneumococcus, streptococcus scarlatinae, or streptococcus erysipclatis. Furthermore, we have been unable to demonstrate in the serum of any rheumatic fever patient a specific agglutinin or precipitin against the homologous streptococcus previously recovered from his blood or lesions. We¹⁵ have been able to demonstrate complement binding antibodies against the nucleoproteins of streptococci, both green and hemolytic, but could find similar antibodies in the serum of convalescent pneumonia patients and in apparently normal individuals. R. C. Lancefield,⁷ in our laboratory, has shown that this cross fixation is probably due to the immunological similarity of nucleoproteins of hemolytic streptococci, nonhemolytic streptococci, pneumococci, and, to a smaller extent, of staphylococci. It is, therefore, impossible to use positive results obtained in complement-fixation tests with antigens containing nucleoproteins of streptococci as conclusive proof that they are the etiological agents; in other words, it is difficult, if not impossible, to use the complement-fixation reaction to detect specific infections with hemolytic and green streptococci. Nevertheless, recent interesting and important studies concerning the nature of streptococcus infections indicate how necessary it is to maintain an open mind as to the relationship between these microorganisms and rheumatic fever.

In the absence of a specific etiological agent or of an immune reaction to give us an indication of uniformity of this disease we are forced to search elsewhere for this clue. Histo-pathology in this respect has furnished us with valuable information in more than one disease. For example, in syphilis the perivascular granuloma is the general type of response to the irritating action of the *Treponema pallidum*. Straus¹³ has defined tuberculosis as a general disease characterized by miliary eruptions in various organs. One might paraphrase this definition in describing rheumatic fever as a general infection characterized by submiliary nodules in certain organs. In the rheumatic heart as already mentioned this nodule has its most characteristic appearance as the Aschoff body; it may be interpreted as a focal interstitial inflammation, situated in the tissue around the smaller arteries and arterioles; there is both a stimulation of fixed cells somewhat similar to the endothelioid cells of the tubercle and an invasion of wandering cells. The peculiarity of the lesion is the presence of "irritation cells"—giant cells of a different type than those seen in the tubercle. There is practically always necrosis of the center of the nodules as well as of the contiguous muscle fibers. The healing of the lesion is attended with scar formation.

While the picture of the Aschoff body is not completely reproduced in the other focal lesions of rheumatic fever, the differences can be largely explained upon differences in the tissue involved and the presence of a superimposed exudative process. In the mural

endocardium nodules identical in appearance have been found; their presence in great numbers in the left auricle has recently been shown by MacCallum⁸ to give a peculiar gross appearance to the lining structures. It seems to us that essentially the same process is responsible for the valvular changes. In most descriptions of rheumatic endocarditis the chief stress is laid upon the very obvious verrucæ; but careful microscopic examination of the entire valve practically never fails to reveal important interstitial changes occurring throughout the major portion of the leaflets. The existence of blood vessels and of areas of inflammation in long-standing rheumatic valvulitis is well recognized and has been explained as secondary to the injury of the endocardium and formation of verrucæ. This conception predicates that the initial injury of the valve is due to the deposition of the causative agent in the cells of the valvular endothelium, then a death of the contiguous structures, followed by a deposition of the various thrombotic elements from the blood stream to form the verrucæ. Recently we have had the opportunity of examining the tissue from 4 patients dying of this disease within two or two and a half weeks of the appearance of the arthritis; in 3 the attack was the first one noted by the patient; in the fourth it was the second. In the first no verrucæ were detectable macroscopically, but many typical submiliary nodules were found in the valves and adjacent chordæ; numerous areas of perivascular inflammation were present throughout a thickened valve; and occasionally definite endarteritis was discernible in the smaller vessels. The entire valve was swollen; but only in one small area of the endocardium was there evidence of necrosis and early verruca formation. The second case showed similar vascular changes and areas of focal inflammation throughout the valvular tissue, a few typical submiliary nodules and slightly larger flat verruca formation in one small area. In the third patient the fatal issue occurred during tonsillectomy on the nineteenth day when it was felt that he had entirely recovered from the acute disease. A small verruca was found at only one place on the aortic valve, but in the substance of the valve there was distinct evidence of mild interstitial inflammation. The death of the fourth patient occurred on the fourteenth day of the second attack of the disease. Grossly no vegetations were seen on any of the valves, but microscopically there were present many foci of intense infiltration with polymorphonuclears, lymphocytes and a few large endothelioid cells. In a few small areas there was desquamation of the valvular endothelium and very slight deposit of fibrin which was interpreted as early evidence of verruca formation.

From the clinical study of rheumatic polyarthritis we know that swelling due to the exudation of edema fluid and wandering cells can be a marked feature of the inflammatory response. In the valves above described there was also evidence of a similar swelling.

It seems to us, therefore, that the primary reaction in rheumatic disease of the valves is in the interstitial tissue, and that the verrucæ are usually due to the deposition of thrombi on a portion of the valve where the vitality of the endothelial and subendothelial layers of the endocardium has been impaired as a result of repeated impacts with the contiguous valve. This theory of death of the endocardium being due to mechanical trauma of an already inflamed structure offers a rational explanation of the localization of the vegetations at a distance from the free margin of the valve. It is also possible that single small verrucæ might form at a point where a submiliary nodule broke through the endocardium. Cary Coombs³ has marshalled convincing evidence that interstitial valvulitis is the important feature of rheumatic endocarditis.

The recent extensive investigation of Pappenheimer and Von Glahn¹⁰ indicates that essentially the same type of response is ordinarily present in the aorta of patients dying as a result of rheumatic carditis. Upon first glance it might seem that pericarditis was an entirely different process; but in inflammations of this structure the outpouring of serum and fibrin is the usual response to injury whether this be due to the tubercle bacillus or to the causative agent of rheumatic fever. The thick layers of fibrin and subsequent organization may mask the primary lesion; but we have found in the pericardium bodies closely resembling Aschoff bodies, and in the fibrous tissues of adherent pericardiums active perivascular focal reactions closely resembling those found in sclerotic valves.

In the subcutaneous fibroid nodules we have lesions grossly more comparable with tubercles. When excised early they have a similar yellowish gelatinous appearance. Microscopically they are seen to consist of central areas of necrosis containing a small amount of fibrin; surrounding this there are perivascular collections of many large polygonal and branching cells with basophilic protoplasm, lymphocytes, and polymorphonuclear leukocytes in varying numbers. In subcutaneous nodules removed soon after their appearance I¹⁴ have seen polynuclear cells closely resembling the "irritation giant cells" of the Aschoff bodies. Large subcutaneous nodules may be considered as conglomerations of many small submiliary nodules. Poynton and Holmes¹¹ describe perivascular submiliary nodules in the brains of patients dying from chorea. The most rational explanation of the symptoms of chorea is the presence of focal areas of encephalitis. At times the meninges may be involved; but encephalitis may occur without meningitis just as myocarditis may occur without pericarditis.

The response of the tissues about the joints to the virus of rheumatic fever is now known to be essentially the same as that found elsewhere. Both Coombs² and Fahr⁴ have described focal proliferative inflammation in periarticular tissues obtained postmortem from subjects dying from rheumatic heart disease. Recently we¹⁴

have excised bits of joint tissue from patients during the first week of an acute attack and found vascular and perivascular lesions in every respect similar to those present in subcutaneous nodules. When the patient had received no antirheumatic drugs there was, in addition, marked edema of the tissues; when he was fully under the influence of salicylates the exudative features were less prominent, but submiliary proliferative lesions were still easily found.

Combined clinical and histo-pathological studies have, therefore, taught us that there are two general types of response on the part of the body to the invasion of the causative agent of this disease, namely, proliferative and exudative. At the bedside the only visible proliferative lesion is the subcutaneous nodule; but the interpretation of many symptoms and signs as well as of the peculiar course of the disease is made simpler by the knowledge that comparable changes are occurring in important organs. The exudative response, on the other hand, is more evident in the swelling, pain, and tenderness seen in acute rheumatic polyarthrititis. Probably the most characteristic feature of this disease is the disappearance of exudation and the symptoms dependent upon it following the exhibition of sufficient doses of certain drugs. It is well established, nevertheless, that subcutaneous nodules may appear continuously in a patient who is receiving maximum doses of salicylates. The failure of the salicylates to influence markedly the proliferative lesion probably explains why the symptoms of chorea persist and the development of valvular disease continues in patients who are receiving apparently full therapeutic doses of salicylates or neocinchophen.

It may be well to mention certain other peculiarities attending the two types of response; at the same time keeping in mind that usually there are combinations of the two, and that the clinical picture is dependent upon which one predominates. With acute toxic symptoms and high fever one expects to encounter exudative manifestations; as the course becomes chronic the fever is lower and symptoms depending upon the existence of proliferative tissue alterations in the involved organs become increasingly predominant. There are, moreover, cases in which a low grade, chronic course is always the outstanding feature. Doubtless many patients with this type of infection never come under the care of the physician until they have marked cardiac disease. It has been brought to our attention that in many parts of the world there seems to be almost a complete absence of acute articular rheumatism and still mitral stenosis is not infrequent. If we regard this form of valvular disease as practically always of rheumatic origin we may assume that the disease as it exists in those localities assumes a chronic proliferative course from the beginning, either due to the fact that the etiological agent in those regions is more attenuated in character or that the persons affected have an inherently different type of immunity.

It is possible that a changing character of the infection explains the diminution in the frequency of the condition known as acute inflammatory rheumatism; but in this respect it must be borne in mind that the use of salicylates is one of the most common of practices. Indeed, it is almost necessary to write a new clinical description of the disease with the patient under the influence of partial or complete therapeutic doses of the various antirheumatic drugs. A study of the older literature makes it evident that in most instances the infection is self limiting: at times after two weeks, at other times after two, or three months, and in many instances after longer periods. If a patient is kept under the influence of salicylates the obvious clinical manifestations of recurring or continuing infection are often masked. It is necessary, therefore, to document more carefully the slight symptoms that persist, and to resort to more careful instrumental examination of the patient to detect signs that would otherwise escape our notice. Thus we have found that curves of leukocyte counts made at weekly intervals in most cases serve as a fair index of the persistence of infection. It is true that in some patients there were other evidences of active disease even in the presence of repeated normal leukocyte counts; and rarely in others abnormally high counts have persisted in spite of the absence of other evidences of persisting infection. As clinicians, we should recognize the necessity of properly evaluating symptoms and signs and should not disregard certain ones because in some exceptional instances they have not followed the accepted rule.

COMPARISON OF ELECTROCARDIOGRAPHIC EVIDENCE OF MYOCARDIAL DISTURBANCE WITH AUSCULTATORY EVIDENCE OF VALVULAR DISEASE AND PERICARDITIS IN 81 CASES OF RHEUMATIC FEVER.

	Total cases.	Increase in <i>P-R</i> time.				Change in form of electrocardiogram.	Valvular disease.				Pericarditis.
		Number.	With fever.	Without fever.	Incomplete heart block		None.	Doubtful.	Mitral.	Aortic.	
First attack . . .	34	29	22	21	4	33	5	12	16	5	6
Recurring attacks	34	30	24	13	2	29	1	5	28	8 (8?)	3
Cardiac type . .	13	11	10	4	4	13	13	7 (4?)	7
Total . . .	81	70	56	38	10	75	6	17	57	24	16
Per cent	87	69	47	12	93	7	21	70	30	20
							28				

Practically all statistics of the relative frequency of involvement of the heart in rheumatic fever rest upon the occurrence of murmurs which the examiner interpreted as due to deformities of the valves. Pericarditis, obviously, is an indication of very severe cardiac injury. Study of the heart's action with the electrocardiograph has furnished us with evidence that there is some degree of functional disturbance in over 90 per cent of patients suffering from this disease (see Table). While it is impossible to be absolutely certain that these electrocardiographic alterations are caused by structural changes in the heart, and it has been shown that the administration of digitalis, ether, and histamine may produce similar alterations in the electrocardiogram, our knowledge of the histo-pathology of rheumatic myocarditis permits us to assume with a fair degree of assurance that these abnormal electrocardiograms are the result of some injury to heart muscle or conduction system. It should be pointed out that these unusual curves in many instances have been only transitory and that upon recovery from the acute infection the form of the curve and the function of the heart have returned to normal and remained in that condition for many years. It may be that changes in conduction time or in form of the ventricular complex are caused by a transitory edema about a few submiliary foci which of themselves are relatively unimportant. A very valuable conclusion to be drawn from this type of evidence, however, is that the heart is probably affected to some degree in practically every patient suffering from rheumatic fever. This conception should eventually alter our attitude toward the therapeutics of this disease.

Other indications of myocardial implication during the period of acute infection are transitory precordial pain and hyperesthesia, and the occurrence of abnormal rhythms; among these the most common is gallop, apparently caused by a marked exaggeration of the normal third heart sound. We have noted repeatedly that such gallops were accompanied by distinct alterations in the form of the electrocardiogram. The interpretation of the murmurs so frequently heard during this disease must often await the results of observations extending over months. The point to be especially emphasized is that a search for murmurs is only one of a number of examinations it is necessary to make in order to detect evidence of cardiac derangement.

It has long been recognized that an impaired nutritional state was a feature of the rheumatic infection. Clinical descriptions made in the presalicyl era indicate that marked emaciation was frequently seen in those patients with the subacute and chronic form of the disease. One distinct benefit from antirheumatic drugs is that with the control of the fever and its concomitant toxic state the tendency for the patient to lose weight is less marked. The weight curve, nevertheless, is still a good auxiliary guide in helping us to determine whether or not the patient is succeeding in overcoming

his infection. Not infrequently one notes a continual loss in weight when other symptoms seem to be fairly well controlled by salicylates; also relapses are often heralded by declining weight. There is a more or less common, but unfounded belief that errors in diet or metabolism are important etiological factors in rheumatic fever. These opinions arose from the lactic acid theory of rheumatism, from confusion with gout, and lately from the hypothesis that arthritis is due to a high blood sugar. As a result of these opinions has arisen the practice of omitting fruit to eliminate certain organic acids, red meat "to combat uric acid," and reducing carbohydrates to lower blood sugar. As a result of this régime many of the patients suffer from undernutrition with a consequent deleterious influence on their natural powers of resistance.

Assisting a patient to overcome his infection by increasing his general nutrition has been shown to be one of the most important therapeutic measures in tuberculosis. Maintaining or increasing a typhoid fever patient's weight has been shown to shorten the period of convalescence from that disease. In our experience the maintenance of nutrition is one of the most important therapeutic measures for rheumatic fever.

Analysis of a large series of charts of rheumatic fever patients, in which have been documented all of the signs and symptoms as well as the various laboratory records of activity of infection, has convinced us that the drugs we have been considering as specifics are probably antisymptomatic in their action; and that if patients are carefully studied while under their influence not infrequently signs of persisting infection will be discovered. By means of salicylates or neocinchophen, distressing symptoms of arthritis are fairly easily controlled and high fever is eliminated with a corresponding reduction of the pulse rate. This doubtless spares the heart in more than one respect. If edema is eliminated from the valves by the drugs in the same manner as from the periarticular tissues it is conceivable that the endocardium might be spared some of the traumatic injury to which we think a swollen valve especially liable. A 20 or 30 per cent reduction of the heart rate reduces the number of impacts of the injured valve by a corresponding amount.

All of these are desirable aims of therapeusis; but if in attaining them the patient is led to believe that he is cured of his infection, or the physician is blinded to the pathological processes that are persisting in spite of the absence of obvious symptoms, the patient may in the end suffer as much permanent injury to some important organ as if he had passed untreated through an attack of the disease. Probably most physicians can remember many patients who have been allowed to be up and about in the wards or in their homes while under the influence of therapeutic doses of salicylates or neocinchophen, and who had relapses when these drugs were discontinued. A common practice is to discharge from the hospital patients while

under the influence of these drugs. The reason for this is obvious. The physician often believes that the elimination of symptoms by salicylates is a sign of eradication of the disease; and in a desire to turn over the service as rapidly as possible the doctor yields to the importuning of an apparently well person to return to his home. We may profitably revert to our comparison of syphilis and rheumatic fever in their response to certain drugs. The disappearance of gummata following the administration of iodids was not a sign of the elimination of the treponema from the patient; nevertheless iodids have an important place in the treatment of a patient with syphilis and often help in saving an important organ from irreparable damage. Other therapeutic measures must, however, be applied if the patient is to be cured. Similarly in the treatment of rheumatic fever the beneficial effects of salicylates must be complemented by other measures which have been shown to be of benefit in combating infection.

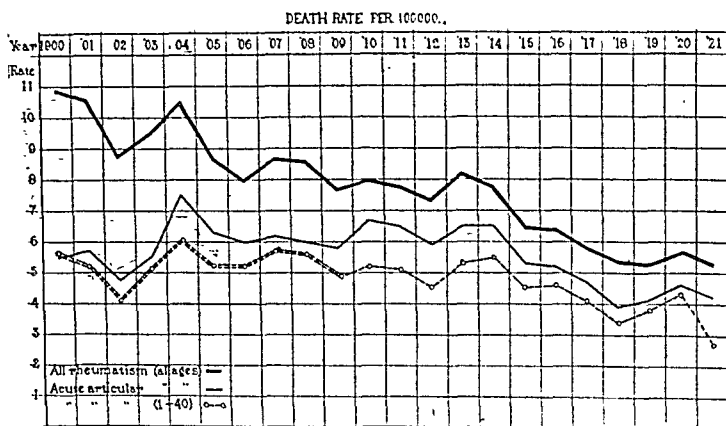


CHART I.—Death rate from all rheumatism, and from acute rheumatic fever in New York State, 1900–1921.

At this point it may be asked what have been the influences of our drug therapy upon the development of chronic cardiac disease, as well as upon the death rate from rheumatic fever itself. Both the impressions of physicians and vital statistics seem to indicate that the death rate from rheumatic fever is less than in former years (see Chart I). Death during the acute stages of rheumatic fever is usually due to one of three causes: Hyperpyrexia, severe general intoxication, and acute heart failure resulting from severe myocarditis. Doubtless the use of the drugs at our disposal has been instrumental in eliminating to a large extent the first two of these lethal complications. The lower death rate may be due, therefore, in part to a decreased incidence of rheumatic fever as a result of the application of general hygienic measures and also to better treatment during the acute stages with a consequent result that the condition is one that is recorded as cardiac disease instead of rheumatic fever.

The failure of health departments to make rheumatic fever reportable leaves us without any source of information as to whether or not there is a decreased incidence of this disease. Likewise our ideas as to trends in the incidence of heart disease must be based upon mortality rates. In the Registration Area of the United States, vital statistics show that deaths from cardiac disease of the entire population is steadily increasing; but these trends can be explained to a certain degree by the fact that as the expectation of life increases there is more opportunity for the degenerative cardiovascular conditions to be an increasingly important factor in the death rate. If we are to obtain an approximate idea of the trends in rheumatic

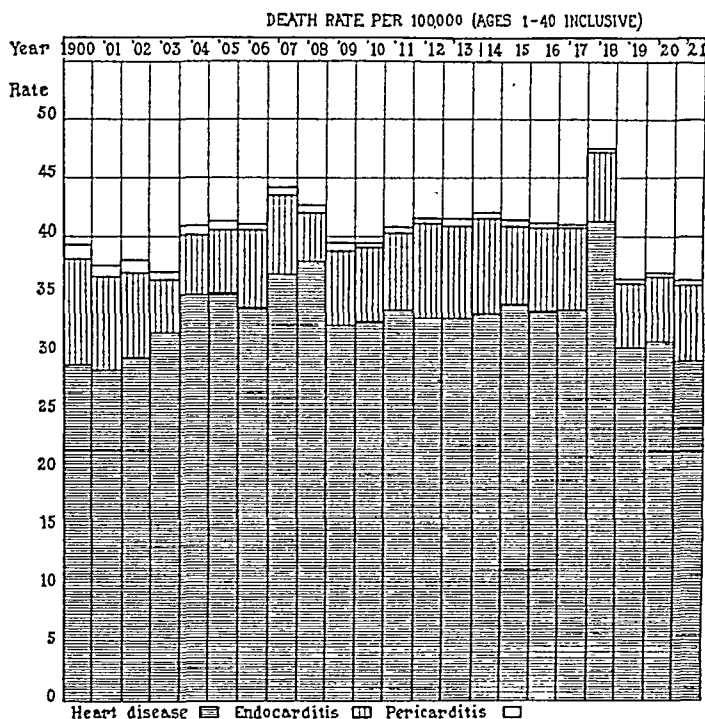


CHART II.—Specific death rates (ages one to forty years inclusive) for heart disease, endocarditis and pericarditis in New York State, 1900-1921.

heart disease we must select age periods when we think the rheumatic infection is the most active. Analysis of the deaths from heart disease, endocarditis and pericarditis in New York State from the years 1900 to 1921 show practically no diminution in the rate of this period (see Chart II). Certain distinct cycles are noted with more deaths in the years of influenza epidemics followed by a decrease in the two or three subsequent years, and then a slowly rising rate until the next epidemic. Life insurance data indicate an increasing rate since 1921. Comparison of the death rates from heart disease and pulmonary tuberculosis in New York City in the past six years, shows that in children of school age, heart disease is

now three times more frequently a cause of death than pulmonary tuberculosis, and that in later age groups with the fall in tuberculosis death rates, there is a slight but steady increase in deaths from heart disease. Insofar as vital statistics are of value in judging the effect of our therapeutics, it seems that both the preventative and curative measures so far applied to infectious heart disease have been of little value.

We may well inquire the reasons for this failure, and ask whether conditions may be remedied.

Successful prevention of an infection depends primarily upon a knowledge of the nature of the etiological agent, how it enters the body, where it increases in the body and whence it emerges from the body. Attention has already been drawn to our ignorance of most

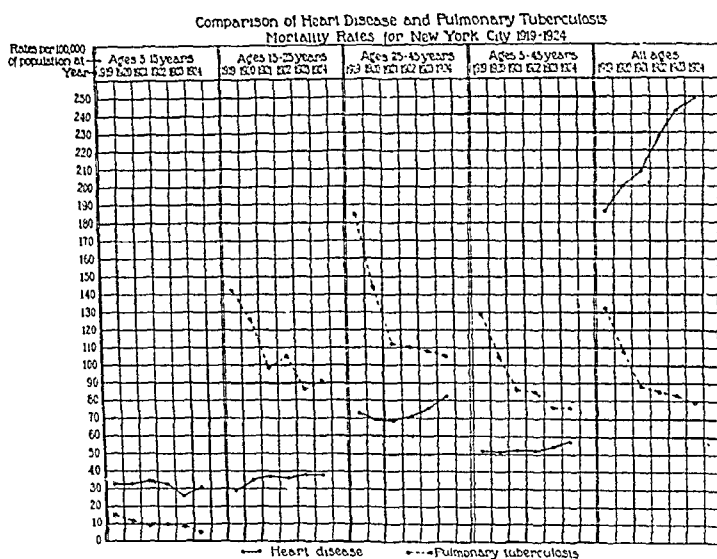


CHART III.—Comparison of death rates from heart disease and pulmonary tuberculosis for certain age groups in New York City, 1919-1924.

of these factors in regard to rheumatic fever. Protective immunization depends upon our ability to manipulate the etiological agent successfully. Chemotherapeutics as applied to prevention of a disease must be founded upon positive demonstration that the drug applied is effective in reaching and destroying the etiological agent and not simply in alleviating symptoms. The successful warfare against tuberculosis has been based not only upon the destruction of the tubercle bacillus in the material in which it was excreted from the body, but also upon a recognition of the chronic nature of the infection and the application of suitable measures to enable the patient to combat that type of infection.

This brings us directly to what I regard as probably the large important phase of treatment of rheumatic fever, namely of war length of time it is necessary to keep the patient quiet. Br

can be stated that this should be as long as signs of infection persist. Recognition of the different types of the disease already mentioned and the determination into which of these types a patient falls is most useful; for it is obviously unwise to keep a patient with a short course of rheumatic fever in bed a long period, and conversely permitting a patient with a drug masked active infection to be up and about is not the best measure to conserve his strength, protect his heart, and increase his powers of resistance.

The period of rest needed is longer than is usually recognized or enforced. A summary of the length of time it was necessary to keep 72 of our patients in the Rockefeller Hospital is shown in Chart IV.

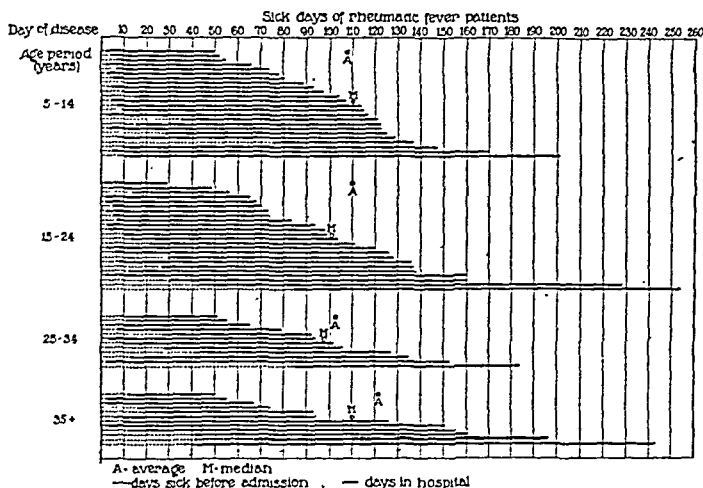


CHART IV.—Number of days spent in hospital by 72 patients with rheumatic fever, before they were able to go to a convalescent home. Each line represents time of 1 patient.

This period was only that spent in hospital and does not include an average of from two to six weeks in a convalescent home after leaving the hospital.

Let us make clear that these patients were treated according to the accepted methods, that is, antirheumatic drugs for arthritis and high fever, removal of such diseased foci as tonsils and teeth, and treatment of sinuses or other possible infected foci. Our special care was to keep patients quiet until signs of active infection had passed.

If general hospitals kept their patients with rheumatic fever for periods similar to this there would be none other than rheumatic fever patients in the wards during the winter and spring months. The question to be met is: "How can these patients be given proper periods of rest?" In this one point of proper provision for rest an incident in the institutional and sanatorium treatment of tuberculosis heart hinted a way. Perhaps the time may come when the tuberculous problem has been completely solved and these sanatoria will

be converted into hospitals for the treatment of patients with rheumatic hearts; but before that time it is to be hoped that provision for the proper care of a large group of these patients will have been made. A few heart hospitals where proper study of these problems could be both intensively and extensively carried out would do much toward formulating a definite plan in the treatment of a condition which up to the present has been but little permanently benefited by the methods now in vogue.

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CLINICAL OBSERVATIONS ON THE VALUE OF CALCIUM CHLORID AS A DIURETIC AND ON ITS INFLUENCE UPON THE CIRCULATORY MECHANISM.

(SEVENTEEN CASES OF CARDIAC FAILURE, ONE OF TUBERCULOUS EFFUSIONS IN SEROUS CAVITIES, ONE OF HEPATIC CIRRHOSIS WITH ASCITES AND TWO NORMAL CONTROLS.)

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Literature. In 1918 Schutz reported beneficial results from small doses of calcium chlorid administered by mouth in cases of congestive heart failure. ^{as} ^{resis} ^{am-} ^{wever,}

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nephritis with edema. In a number of his cases this therapy alone did not cause diuresis, but on the addition of digitalis a marked diuresis resulted with the reduction of edema. He inferred from these observations that calcium chlorid did not affect the cardiac factor in the etiology of edema in these cases.

On the other hand, Singer in 1921 found that the intravenous injection of calcium chlorid (0.5 gm.) or the oral administration of calcium lactate (3 gm. per day) caused a temporary diuresis in cases of cardiac failure as well as in so-called cardiorenal cases with edema. He observed that these calcium salts also caused temporary strengthening of the heart action, slowing of the heart rate and lowering of blood pressure. He also states that the best results are obtained by giving these calcium salts and digitalis simultaneously. Cheinisse also reports that calcium chlorid given intravenously in doses of 1 cc. of a 10 per cent solution is a good adjuvant to digitalis in cases of cardiac failure with edema.

More recently, Walters and Bowler investigated the effect of intravenous injection of calcium upon the heart experimentally in normal and jaundiced dogs. They found that therapeutic doses (82.5 mg. per kilogram of body weight injected in a 10 per cent solution at the rate of 1 cc. per minute) quickened the pulse somewhat but they did not find any change in blood pressure even during gradual increase of the dose to the lethal amount by the gradual injection of the 10 per cent solution at the rate of 1 cc. per minute. Lethal doses caused tachycardia, ectopic origin of impulses, disturbances in conduction and finally ventricular fibrillation followed by death of the animal. They refer to the occurrence of tachycardia and the sensation of flushing of heat all over the body in patients during the intravenous administration of calcium chlorid. However, with Hirschsohn and Maendl, they attribute these phenomena to the "dynamic effect" of intravenous injection *per se*, for similar phenomena have been observed following the injection of solutions of quinin, dextrose, hexamethylenetetramin and urea. It is probable that the observations made by Singer correspond to this temporary reaction.

Blum and his collaborators have reported results which indicate that calcium chlorid is an effective diuretic and causes elimination of fluid from serous cavities in cases of inflammatory effusions in the pleural sacs or in cases of hepatic cirrhosis with ascites. Krummenacher and others have reported similar results. Blum and his collaborators, however, sounded a warning against the use of calcium chlorid administered by mouth in cases of edema of cardiac failure, since in their experience the condition of such patients became aggravated as a result of this therapy.

an inçenberg recently reported investigations which led him to heart ble that in small doses of 0.1 to 1 gm. calcium chlorid has a past si.ivic but no diuretic action, whereas this latter effect takes

place only after the administration of doses larger than 1.5 gm. From these premises he infers that the diuresis caused by calcium chlorid is not due to its cardiotonic influence.

In 1920 Denis and Minot drew attention to the fact that the upper level of calcium content of blood serum tends to be fixed and could be raised for but a very short period of time (if at all) by the ingestion of large quantities of calcium chlorid. Their observations have been repeatedly corroborated by other investigators. It would seem, therefore, that a continued diuretic effect during and after calcium chlorid administration by mouth is not the result of increased calcium content of the blood.

In 1911 Meyer and Cohn showed that the oral administration of calcium salts to normal infants causes decrease in weight due to loss of water from the body. These investigators found that the calcium ion is excreted mainly in the stool, that the chlorin ion combines with other bases and that the resulting chlorids are excreted in the urine. More recently, Jansen has shown that even after intravenous injection of various calcium salts, including calcium chlorid, the calcium ion is largely excreted in the stool.

In 1921 Vlum and his colleagues found that with the administration of calcium salts, when no diuresis occurred, sodium was retained, while during diuresis an increase in sodium excretion was found. This they attributed to the antagonistic action between the calcium and sodium ions. They therefore advocated the use of salt-free diet together with calcium chlorid in the treatment of nephritis with edema.

Atchley, Loeb and Benedict studied a case of diabetic coma with edema treated by the oral administration of large doses of calcium chlorid per day, and observed a marked diuresis which began at the end of the first twenty-four hours of this therapy. They found the chlorin ion was excreted largely in the form of ammonium chlorid, while sodium excretion was also increased. They compared the data in this case with the data in a case of diabetes with spontaneous diuresis and found no essential difference. They also studied the effect of 20 gm. of calcium chlorid given by mouth to a normal individual; in this case marked diuresis occurred and they found an increase in the amount of sodium, chlorin, potassium and ammonia excretions.

Haldane, Hill and Luck also found increased ammonium chlorid excretion following the ingestion of large doses of calcium chlorid by a normal person. They believe that the diuresis may be due to lowering of osmotic pressure in the tissues, which is caused by disturbance of the Donnan equilibrium as a result of the slight acidosis developed during the ingestion of large doses of calcium chlorid. Gamble, Ross and Tisdall offer a similar explanation for the diuresis which results from the administration of hydrochloric acid, ammonium chlorid and calcium chlorid. Most recently, however,

Salvesen, Hastings and McIntosh have reviewed the subject of the effect of calcium salts on the inorganic composition of the blood, and from their work as well as from that of others they conclude that the question whether the diuretic effect of calcium salts is dependent on the anion and is in some way connected with the production of acidosis is as yet unsettled.

Rockwood and Barrier report 7 cases of edema of nephritic and diabetic origin treated by the oral administration of calcium lactate or calcium chlorid or both in doses of 12 to 18 gm. per day. Marked diuresis occurred as a result of this therapy in 6 cases; in the seventh diuresis occurred but was not attributed to the calcium therapy. They also found that large doses of calcium chlorid do not increase the amount of serum calcium. In several cases the chlorid was more effective than the lactate salt and they conclude that the former is the better diuretic. Keith *et al.* also report a significant diuresis in 1 case of subacute glomerular nephritis and in 1 of nephrosis.

This brief review of the literature indicates that calcium salts may cause diuresis in normal individuals as well as in individuals with a variety of diseases, including nephritis, cardiac failure, diabetes with edema, inflammatory effusions in the pleural sacs, hepatic cirrhosis with ascites and others. The influence of the calcium salts given orally in therapeutic doses seems to be related to the metabolism of water and inorganic salts in the tissues rather than directly to its effect upon the circulatory mechanism.

Our interest in studying the value of calcium chlorid as a diuretic was aroused by the striking results obtained in a case of heart disease with congestive failure and edema (Case III) when, after digitalis, diuretin and calomel began to fail or to be sluggish in their diuretic effect, calcium chlorid was most effective.

The chief object of our investigation has been to test the value of calcium chlorid as a diuretic and to determine its effect upon the circulatory mechanism as measured by clinical methods, particularly with reference to a possible digitalis-like action.

Present Investigation. Method. Crystalline calcium chlorid was administered in the form of a solution almost invariably, in 2.5 gm. doses diluted in 50 to 100 cc. of water. In experiments upon a normal individual doses of 5 gm. and 8 gm. each were taken. In the majority of cases the daily amount consisted of 15 gm. given in 6 doses of 2.5 gm. each at two-hour intervals. With the smaller doses the only handicap was the unpleasant taste of the drug; this may be avoided by giving the dry salt in capsules, each containing 0.5 gm. The larger doses of 5 and 8 gm. each caused a burning sensation in the epigastrium which was readily relieved by taking some food, less readily by drinking water. Diarrhea did not occur in any case; rather was there a tendency to constipation.

The "fluid intake" includes only liquids, like soups, milk, water, and not the water in solid or semisolid foods. In all but 2 cases

(II and XVII) the diet was a mixed ordinary hospital diet and salt was not restricted. In the few cases in which salt intake was restricted this fact is mentioned.

The pulse rate represents the resting pulse rate taken in the morning before breakfast at about seven o'clock.

The blood pressure was recorded by the auscultatory method and in cases of auricular fibrillation the point at which beats of an average rate of 80 to 90 per minute were first heard was recorded as the systolic pressure and that point at which beats at a similar rate ceased to be heard or became very faint was recorded as the diastolic blood pressure.

Vital capacity was determined with an ordinary water spirometer and is expressed in the tables in the terms of cubic centimeters of air, thus furnishing evidence of changes in the individual case.

By the term "digitalization" is meant the administration of 0.1 gm. digitalis leaf per 10 pounds of body weight within forty-eight hours and the usual maintenance dose prescribed in our clinic is 0.1 gm. of digitalis per day. Almost invariably digitalis leaf in pills of 0.1 gm. each is the preparation used; in a few instances digifolin was administered by mouth or intramuscularly.

Diuresis in Normal Persons During Calcium Chlorid Administration.

CASE I.—H. N. S., male, aged twenty-six years. In order to determine the effect of calcium chlorid when administered to normal individuals with no cardiac or renal disease, two volunteers took the drug. The first series of observations on Case I were made under the following conditions: low calcium and salt-poor diet, which contained 0.093 to 0.140 gm. calcium and 1 to 2 gm. sodium chlorid per day, with a calorific value of 10 per cent or more over the basal requirements; continuation of subject's usual activities throughout the fifteen days of the experiment; blood pressure and vital capacity determined at midday before luncheon. The relatively low daily fluid intake of the subject during this experiment is his normal fluid intake. The calcium chlorid was taken in doses of 5 gm. diluted in 100 cc. of water three times a day with each meal for two days, on the third day 15 gm. in 200 cc. of water in one dose with the midday meal and during the next three days 8 gm. in 125 cc. of water three times a day, with each meal. Thus a total of 117 gm. was taken in six days.

The subjective symptoms were chiefly related to the unpleasant taste of the solution of calcium chlorid and the sensation of burning referred to the epigastrium which followed the larger doses. This discomfort lasted for one-half to one hour. With the smaller doses of 5 gm., each taken with a meal after about half of the food had been consumed, there was no epigastric burning. Occasional griping occurred during the days when the larger doses were being taken and there was a tendency to constipation; at no time did diarrhea occur.

The data in Table I show evidence of some diuresis during the course of calcium chlorid ingestion. The daily changes in the electrocardiogram are not conclusive evidence of the effect of calcium chlorid administered by mouth since similar changes occurred before and after this therapy.

TABLE I.—EFFECT OF CALCIUM CHLORID INGESTION IN A NORMAL PERSON. (CASE I.)

Date. 1923.	Calcium chlorid, gm.	Fluid intake, cc.	Urine, cc.	Body weight, kilos.	Blood pressure.		Vital capacity, cc. air.	Heart rhythm.	Electrocardiogram.		T wave in Lead II, mv.
					Sys.	Dia.			Rate.	P-R interval second.	
Nov. 20	0	780	720	70.0	109	64	3600	Normal	80	0.16	+0.65
21	0	790	720	70.0	115	68	3600	Normal	70	0.16	+0.65
22*	0	790	700	70.0	110	65	3620	Normal	75	0.16	+0.70
23	15	790	820	70.0	120	70	3640	Normal	90	0.15	+0.50
24	15	780	1240	70.0	112	64	3700	Normal	70	0.17	+0.80
25	15	720	960	69.5	115	65	3690	Normal	80	0.16	+0.75
26	24	900	720	69.5	115	68	3800	Normal	75	0.17	+0.70
27	24	1420	2400	69.0	115	70	3790	Normal	70	0.17	+0.65
28†	24	960	1560	68.5	108	62	3800	Normal	75	0.17	+0.75
29	0	1200	1500	68.5	110	65	3810	Normal	90	0.16	+0.45
30	0	960	1250	69.0	112	65	3800	Normal	75	0.16	+0.45
Dec. 1	0	1000	950	69.0	115	71	3800	Normal			
2	0	920	800	70.0	115	61	3800	Normal			
3	0	960	720	70.5	110	60	3810	Normal			

* 8.5 mg. calcium per 100 cc. blood.

† 8 mg. calcium per 100 cc. blood.

TABLE II.—EFFECT OF CALCIUM CHLORID INGESTION IN A NORMAL PERSON. (CASE I.)

Date. 1924.	Fluid intake, cc.	Urine, cc.	Calcium chlorid, gm.	Date. 1924.	Fluid intake, cc.	Urine, cc.	Calcium chlorid, gm.
Mar. 18	2160	900	0	April 1	2100	1400	0
19	2100	950	0	2	1200	1400	0
20	2100	1150	0	3	1700	1100	0
21	1800	750	0	4	1600	900	0
22	1500	660	0	5	1800	850	0
23	2100	1200	0	6	1700	800	10
24	2000	1000	0	7	2100	650	10
25	2000	1400	0	8	2200	1350	10
26	1900	1300	0	9	2000	1300	10
27	1400	700	0	10	1900	1500	10
28	1400	600	0	11	2000	1400	10
29	1800	780	0	12	1900	1350	10
30	1800	900	0	13	2000	1400	10
31	1800	1500	0	14	1800	1200	10

There was apparently no significant change in vital capacity or blood pressure and none in the rate or rhythm of the heart; no extrasystoles were noted.

In Table II are represented the results in the same subject on a liberal mixed diet, a forced intake of 2 liters of water per day, and only 10 gm. of calcium chlorid per day. Only a tendency to diuresis is evident.

Acidosis was quite pronounced in this subject during the administration of the calcium chlorid, as proved by laboratory tests.

CASE II.—A. E. K., male, aged twenty-seven years, the second volunteer, also had a liberal diet and took about 2 liters of fluid per day, which is the amount he usually consumes. It is interesting to note that he eliminated about four-fifths of his fluid intake per day, under normal conditions. Calcium chlorid was administered in solution, 5 gm. in 100 cc. of water per dose, and 2 such doses were taken per day, one at the midday meal and the other at the evening meal. On the second day of this therapy a marked diuresis occurred. This however continued only for another day, then ceased and did not recur during the remaining seven days of calcium chlorid therapy (see Table III).

TABLE III.—EFFECT OF CALCIUM CHLORID INGESTION IN A NORMAL PERSON. (CASE II.)

Date. 1924.	Calcium chlorid, gm.	Fluid intake, cc.	Urine, cc.	Date. 1924.	Calcium chlorid, gm.	Fluid intake, cc.	Urine, cc.
Mar. 18 . . .	0	2100	2100	April 3 . . .	0		
19 . . .	0	2100	2150	4 . . .	0	2000	1875
20 . . .	0	2100	1900	5 . . .	0	2000	1800
21 . . .	0	2100	1900	6 . . .	0	2100	1900
22 . . .	0	2100	1900	7 . . .	10	2100	1875
23 . . .	0	2100	1925	8 . . .	10	2100	3200
24 . . .	0	2100	1625	9 . . .	10	2100	3000
25 . . .	0	1900	1700	10 . . .	10	2100	1800
26 . . .	0	1200	1400	11 . . .	10	2100	2000
27 . . .	0	2100	2100	12 . . .	10	2100	1820
28 . . .	0			13 . . .	10	2000	1490
29 . . .	0	2100	1800	14 . . .	10	2100	1900
30 . . .	0	2100	1800	15 . . .	10	2100	1900
31 . . .	0			16 . . .	10	2100	1750
April 1 . . .	0	1800	1450	17 . . .	10	2100	1800
2 . . .	0	2100	1900				

Discussion. In these two normal individuals the diuresis was slight or moderate in degree and its duration varied. Thus in Table I the diuresis is seen to begin on the second day of calcium chlorid therapy and to continue for two days after discontinuation of the drug. In Table II, however, it is seen that only slight if any diuresis occurred in the same subject with the administration of 10 gm. of calcium chlorid per day. The other normal subject, A. E. K., had a striking diuresis on the second day of calcium chlorid therapy but this ceased quite suddenly and in spite of continued ingestion of the drug there was no further diuresis.

Effect of Calcium Chlorid in Cases of Cardiac Failure. CASE III.— N. C. M., male, aged fifty-three years, a merchant, always very active, began to notice dyspnea on exertion in 1921. In February, 1922, his doctor found him to have a systolic blood pressure of 170. Cardiac failure with edema of the legs, ascites and congestion of the lungs first occurred in May, 1922, when he was found to have hypertensive heart disease with a blood pressure of 260 systolic and 160 diastolic. He subsequently had frequent recurrences of congestive failure. There was no evidence of chronic nephritis. He was digitalized in May, 1922, and continued to take an average of 0.2 gm. of digifolin per day. In addition to rest in bed and digitalis, diuretics were always necessary in the treatment of the attacks of congestive failure with general anasarca. He responded very readily to calomel, 0.7 to 1 gm. per day for three days; sometimes diuretin or theocin was given following a course of calomel. These diuretics produced very marked diuresis, as much as 6½ liters of urine a day being passed until all the edema, ascites and hydrothorax disappeared.

In April, 1923, he became less responsive to these diuretics and continued to gain weight, with increasing edema even while taking calomel. A diuresis followed the second of two courses of calomel. Edema did not completely disappear and diuresis having ceased after the second of these two courses of calomel it was decided to try calcium chlorid; this was the first case in which we used this drug as a diuretic.

Well-marked diuresis occurred promptly after the beginning of and during the administration of calcium chlorid by mouth and stopped when this was discontinued only to begin again with resumption of the calcium chlorid therapy. Moreover, a constant negative fluid intake and output balance was maintained by the regular administration of calcium chlorid by mouth, 10 to 15 gm. every other day alternating with 0.2 gm. of digitalis. This régime was continued for two weeks after he left the hospital, then he took digitalis 0.2 gm. every day and calcium chlorid 12 gm. only once a week. He remained free from edema for about six weeks and then in spite of daily doses of digitalis (0.2 gm.) and calcium chlorid (12 gm.) he again developed general anasarca and died on July 23, 1923.

This patient derived much benefit from diuretics. When calomel, theocin and diuretin began to fail in their effectiveness, calcium chlorid produced very prompt diuresis. These results led us to try the use of calcium chlorid as a diuretic in other cases of cardiac failure with edema as well as in 1 case of polyserositis and in 1 case of ascites due to cirrhosis of the liver, conditions in which a number of investigators have reported calcium chlorid to be an effective diuretic.

CASE IV.—J. B. (Hospital No. 260088), male, aged fifty-one years, a coal miner, noticed the gradual onset of shortness of breath on exertion in 1921. After "a cold" in February, 1922, he had swelling of the legs; general weakness and shortness of breath became more marked. After a rest of two weeks he felt better, but not well enough to return to coal mining. He changed his occupation to shoe repairing. In September, 1923, dyspnea and general weakness were very marked; edema of the extremities and "filling up" of the abdomen recurred. After three weeks of rest and treatment with "medicines" he felt well enough to be up and about. In November, 1923, he again became "sick" with swelling of the legs and abdomen; during two weeks of treatment at home with rest in bed and "medicines" he grew steadily worse so that he was brought to the hospital in a desperate condition. He appeared to be in a moribund state, with very intense cyanosis, marked general anasarca, ascites and hydrothorax. There was no evident enlargement of the heart, the blood pressure was 120 systolic and 90 diastolic, the heart sounds were of fair quality, and there was no evidence of valvular or pericardial pathology; there were frequent extrasystoles with pulsus bigeminus for long periods of time (hours). He had marked emphysema and this condition together with possible anthracosis were considered as important factors in the causation of the deep cyanosis.

Soon after his arrival in the ward abdominal paracentesis was performed and a liter of pale straw-colored fluid was removed; 0.8 gm. of digifolin were administered intramuscularly during the first twenty-four hours and because he had nausea only 0.2 gm. of digitalis leaf per day was given during the next three days. This had no noticeable beneficial effect: on several occasions he lapsed into unconsciousness with very weak pulse and intensified cyanosis; the prompt administration of oxygen by the simple funnel method seemed to revive him.

On the eighth day after his admission to the hospital calcium chlorid therapy was started. From the data in Table II it appears that marked diuresis occurred during this therapy and the hydrothorax disappeared; the patient's general condition improved with dramatic rapidity. At the end of three weeks' stay in the hospital he was able to be up and about the ward. There was no perceptible diminution in cyanosis, the blood pressure remained at a relatively normal level, two attacks of paroxysmal fibrillation occurred and ventricular extrasystoles persisted, but were less frequent. There was no change in the size of the heart as measured by percussion, and the heart sounds did not become altered. He became much less orthopneic and the vital capacity increased by more than 300 per cent; whereas the pulse was relatively rapid before marked diuresis began, it became slow and less fluctuating in rate during and after the diuresis. It is doubtful whether this was the result of the action

of calcium chlorid on the heart directly. During the administration of this drug for five days prior to the onset of marked diuresis the pulse remained as it was before calcium chlorid therapy was begun. The diminished frequency of ventricular extrasystoles also began only after the onset of diuresis and it is presumed as most likely that in this case the reduction in number of extrasystoles may have been due to either the excretion of all digitalis which the patient had taken before and after his entrance into the hospital, or, if digitalis was not the cause of the extrasystoles, to improvement in circulation by reduction of edema *per se*.

The evidence in this case may be summarized as follows: probable arteriosclerotic heart disease with cardiac failure and marked general anasarca; digitalis given in large doses (probably causing pulsus bigeminus and nausea) failed to cause diuresis or any clinical improvement in the patient's serious condition; five days after the beginning of calcium chlorid therapy a marked diuresis began; this persisted until all the edema, ascites and hydrothorax had disappeared and some diuresis continued for six days after the drug was discontinued; coincidentally with the diuresis the patient's clinical condition changed so that he was able to be up and about. It is presumed from the evidence in this case that if calcium chlorid were responsible for the improvement in this patient's condition its effect consisted in producing a diuresis not primarily by an effect upon the heart itself, but by influencing water metabolism. The improvement in circulation is, therefore, considered as secondary to the reduction of edema.

CASE V.—C. W. C., (Hospital No. 260263), aged seventy-five years, male, janitor, was first observed in 1920 when he was found to have arteriosclerotic and hypertensive heart disease, auricular fibrillation and congestive failure with edema of both lower extremities and congestion of both lungs. He did not complain of dyspnea or orthopnea. Following digitalization and while continuing to take 0.1 gm. digitalis leaf per day he remained free from edema until January, 1923, when he was admitted to the hospital ward with general anasarca. This had been developing during the previous month when he ceased taking digitalis because the supply of pills became exhausted and he procrastinated in buying more of them. Fibrillation continued but the pulse rate was quite low, varying between 50 and 60 per minute, apparently due to an organic lesion causing A-V block. There was no evidence of chronic nephritis.

On the third day after admission a thoracoparacentesis was performed and 1200 cc. of transudate were removed. Two days later calcium chlorid therapy was begun. A prompt diuresis occurred soon after the beginning of and during calcium chlorid administration. There was no appreciable change in heart rhythm or rate, or in blood pressure, and vital capacity increased only

slightly; no change was detected in the electrocardiographic curves which could be ascribed to the effects of calcium chlorid on the heart directly, and it is therefore inferred that the diuresis was caused by the influence of calcium chlorid on water metabolism in the tissues.

CASE VI.—W. G., (Hospital No. 260230), male, aged sixty-five years, clerk. This patient stated that he was in very good health until four days before he came to the hospital (in December, 1923), when he began having a dry cough and discovered that his feet and ankles were swollen. He was found to have arteriosclerotic and hypertensive heart disease, auricular fibrillation and congestive failure with a moderate amount of edema of both legs and feet and some congestion at the bases of both lungs. He also had marked emphysema. There was no evidence of nephritis.

During the first nine days he was merely kept in bed on a liberal diet with restriction of the total fluid intake to 2 liters per day. During this period of time all edema and congestion disappeared but no very marked diuresis occurred. Then, during the administration of calcium chlorid, the fluid intake and output balance changed from positive to negative and continued so until the cessation of this therapy when a positive balance was reestablished and persisted later during digitalization.

In this case calcium chlorid therapy caused diuresis in the absence of any evident edema, without effecting any change in the heart rate or rhythm, or any change in the shape of the electrocardiographic curve or in vital capacity. Furthermore the absence of diuresis during digitalization suggests that calcium chlorid has not a digitalis-like action but that its effect is on water metabolism in the tissues rather than on the circulatory mechanism directly.

CASE VII.—E. M., (Hospital No. 256940), female, aged twenty-four years, housewife, at the age of sixteen had rheumatic fever and two years later, shortly after she was married, became aware of shortness of breath on exertion. Two normal pregnancies and one miscarriage were unassociated with cardiac failure. In the fifth month of the most recent pregnancy she began to have marked dyspnea on going up one flight of stairs, edema of both legs and feet and cough with occasional bloody sputum. She was admitted to the hospital in June, 1923, two weeks after a normal delivery and was found to have rheumatic heart disease with mitral stenosis (marked) and aortic regurgitation (slight), congestive failure with ascites and edema. She also had phlebitis of the left brachial and internal jugular veins. There was no evidence of nephritis.

Digitalization and 4 gm. diuretin, the latter given in one day, had no significant diuretic effect. The administration of calcium chlorid one week later brought about a negative balance of fluid intake and output which continued for one day after the cessation

of this therapy; edema and ascites disappeared. In spite of continuation of digitalis to maintain a state of digitalization a positive balance of fluid intake and output became reestablished. The pulse rate became somewhat slower only after twelve days of rest in bed and nine days after digitalization; there was no significant change in blood pressure.

From the evidence in this case it may be inferred that the effect of digitalis on the circulatory mechanism was not enough to cause diuresis, but that with the aid of the influence of calcium chlorid on water metabolism in the tissues the output of urine was greatly increased and edema and ascites disappeared.

CASE VIII.—R. B., (Hospital No. 253977), male, aged sixteen years. Since the age of seven he had been having recurrent attacks of rheumatic fever and some choreiform movements in the intervals between these attacks. He first came under our observation in January, 1923, with rheumatic fever and was found to have rheumatic heart disease with mitral stenosis and aortic regurgitation. In spite of tonsillectomy which was performed in February, 1923, he had another attack of rheumatic fever the following month while at home. In April, 1923, was again taken into the hospital with rheumatic pericarditis and congestive failure with edema of feet and legs, ascites and congestion at the bases of both lungs; at this time he also developed bronchopneumonia. With rest in bed, salicylates, digitalization and recovery from the respiratory infection, the edema, ascites and congestion of the lungs gradually disappeared and he was again sent home to convalesce, with instructions to continue taking 0.1 gm. digitalis per day in order to maintain digitalization. Contrary to advice, however, he discontinued the digitalis and returned to the out-patient clinic five weeks later with marked ascites, edema of the legs and congestion at the bases of both lungs. He was sent home with instructions for digitalization and constant rest in bed. He took the digitalis but a week later edema had increased and he was more orthopneic than ever before. Consequently he again entered the hospital and the results of digitalis and calcium chlorid therapy were similar to those in Case VII inasmuch as in the presence of normal rhythm digitalis caused little or no diuresis, while calcium chlorid was more effective.

In Table IV are represented the results of the intravenous injection of 75 cc. of a 2 per cent solution of calcium chlorid in this case (VIII); an increased production of urine must have started soon after the injection, for 350 cc. were eliminated within an hour and another 400 cc. in the following two hours. Electrocardiograms taken just before and immediately after the injection of calcium chlorid showed no differences. These results as regards diuresis are similar to those obtained by Dr. Koehler while working in the Massachusetts General Hospital. He has made numerous obser-

vations of this nature and has found that the calcium content of the blood remains slightly elevated only for one-half to one and a half hours after the injection of calcium chlorid and that there is a coincident moderate but definite decrease in the pH of the blood. These observations are in accord with those of other authors who have investigated these problems.

TABLE IV.—INTRAVENOUS INJECTION OF 75 CC. OF 2 PER CENT SOLUTION CALCIUM CHLORID AT THE RATE OF 5 CC. PER MINUTE.

Time, P.M.		Urine, cc.	Electrocardiogram, etc.
3.30	Normal rhythm; rate, 110; <i>T</i> wave in Lead II = -0.1 mv.; <i>P-R</i> = 0.26 seconds.
4.00	75	
4.35 to 4.50	{ Injection of calcium chlorid		
4.55	{ Electrocardiogram; exactly the same as at 3.30.
5.30	Desire to pass urine.
5.45	350	
6.30	310	
7.30	, 90	

Discussion. In all of these 6 cases of cardiac failure with edema some combination of the usual measures of causing diuresis was tried before the administration of calcium chlorid was begun. Rest in bed alone or with digitalization, and sometimes the addition of calomel or diuretin, or both, were either moderately or little if at all effective in reducing the edema. With calcium chlorid therapy, diuresis began on the first to the fifth day and in 3 cases continued for one or more days after the drug was discontinued. No changes occurred in pulse rate, blood pressure or vital capacity which could be attributed to the effect of the calcium chlorid therapy on the circulatory mechanism directly; nor can we unreservedly attribute to it the slight changes in the electrocardiogram. It would appear therefore that calcium chlorid when taken by mouth is not similar to digitalis in its action but causes diuresis by influencing water metabolism in the tissues.

CASE IX.—L. M., (Hospital No. 261196), male, aged fifty-four years, tailor, was a moderately obese man who had had asthma for twenty years. He was first observed in the hospital in 1920, when it was found that in addition to asthma and emphysema he had arteriosclerotic heart disease, angina pectoris (rare attacks) and some congestive failure. His symptoms of dyspnea on exertion, orthopnea, general weakness and slight swelling of the ankles gradually increased in severity. The attacks of angina pectoris became more frequent, as many as four per week. In February, 1924, he was admitted to the hospital with congestive failure, edema of legs and feet and

congestion at the bases of both lungs. There was no evidence of nephritis. The cardiac rhythm was normal.

With rest in bed and an ordinary mixed diet he slowly improved and the edema decreased while the output of urine increased slightly. When calcium chlorid therapy was begun 6 days after admission to the ward some edema over the sacrum was still present, and with the marked diuresis which followed, this and the crackling rales at both lung bases also disappeared. Some diuresis continued for eight days during which the patient received no medication; with the resumption of calcium chlorid administration no diuresis occurred.

The data in this case indicate a diuretic influence of calcium chlorid, although diuresis occurred after the first course and not after the second. During neither period was there any significant change in heart rate or rhythm, in the electrocardiographic curve or in vital capacity which could be attributed to the direct action of calcium chlorid on the circulatory mechanism. If the diuresis during and after the first course of calcium chlorid therapy was due in part to the action of this drug it is fair to infer that the effect was on water metabolism in the tissues and not on heart action.

CASE X.—A. J. P., (Hospital No. 260490), male, aged fifty-two years, butcher, became aware of dyspnea on exertion subsequent to a cold with sore throat, cough and some fever in January, 1924. He continued at work lifting quarters of beef, weighing as much as 150 pounds, until he came into the hospital the following March, when he was found to have arteriosclerotic heart disease, auricular fibrillation and slight congestive failure evidenced by moist crackling rales at the bases of both lungs. There was no ascites or edema of the extremities and no evidence of nephritis.

A moderate diuresis occurred for 2 days with a régime of complete rest in bed only and continued without any significant increase during 10 days of calcium chlorid administration (15 grains daily). The diuresis ceased on the second day after discontinuing calcium chlorid and subsequent digitalization with effective slowing of the heart rate had no diuretic effect.

The heart rate became somewhat slower during rest and calcium chlorid therapy, but a relatively large apex-radial pulse deficit continued until after digitalization. Electrocardiographic tracings showed certain slight but definite changes; the *T* wave in Lead II was isoelectric before and somewhat negative during and after calcium chlorid therapy and the rate of auricular fibrillation became somewhat slower.

There was no significant change in blood pressure and after the patient had become proficient in the practice of forced expiration no appreciable change in the vital capacity occurred.

Restoration to normal rhythm with quinidin sulphate therapy

was not accompanied by any objective signs of improvement in cardiac function, but the patient felt greatly improved. He was no longer conscious of his heart beating and felt "as if everything were normal again."

The evidence in this case indicates that calcium chlorid had little or no influence on the heart muscle, the slowing of the ventricular rate and the slight negativity of the *T* wave in Lead II probably resulting from other causes. The constant rest in bed alone seems to have been responsible for the moderate diuresis although it is possible that calcium chlorid had some additional diuretic influence.

CASE XI.—M. C. F., (Hospital No. 259937), female, aged sixty-three years, cashier, during the summer of 1923 began to notice palpitation on exertion and also had to begin using two pillows instead of one to avoid slight difficulty in breathing at night. Otherwise she felt well and was able to carry on her work as a cashier. Six weeks before coming to the hospital she had a slight cold with several chills and about this time began to notice swelling of feet and legs which extended up to thighs and abdomen in a few weeks. When she entered the hospital in December, 1923, she was found to have arteriosclerotic and hypertensive heart disease and congestive failure with general anasarca. There was no evidence of nephritis. As a result of rest in bed, an ordinary mixed diet, and slight limitation of total fluid intake she had a moderate diuresis, lost much weight, and the edema and ascites entirely disappeared in eleven days. Subsequently, administration of calcium chlorid for three days did not cause any significant diuresis.

This case again illustrates the effect of rest alone in improving cardiac function with consequent reduction of edema. No striking objective signs of improvement in cardiac function were observed, the pulse rate remained between 75 and 85 per minute, but there was some increase in vital capacity and an increase in pulse pressure as a result of increase in the systolic and decrease in the diastolic pressures.

There was slight diuresis on the third, the last, day of calcium chlorid therapy, but none occurred during the previous two days or after the drug was discontinued.

CASE XII.—E. H., (Hospital No. 261936), male, aged thirty-nine years, farmer, at the age of twenty-nine years had an attack of rheumatic fever which caused him to remain in bed for seven months; subsequently he had several milder attacks. At the age of thirty-five he began to notice palpitation and dyspnea on exertion and had to cease working. During the next four years these symptoms became progressively more marked. In January, 1924, two months before he came to the hospital, he took to bed because of marked dyspnea and orthopnea, swelling of legs and abdomen, and cough with bloody sputum.

He was found to have rheumatic heart disease, mitral stenosis and regurgitation, cardiac enlargement and signs suggesting adhesive pericarditis. There were right hydrothorax, congestion in base of left lung, ascites, and edema over the sacrum and of both lower extremities below the hips. The patient appeared very sick; he was cyanotic and markedly orthopneic.

Marked diuresis and subjective improvement developed gradually during a week of complete rest in bed, limitation of fluids, Karrel diet and digitalization. As the anasarca diminished the extent of diuresis waned until a positive fluid intake and output balance became established.

All therapeutic measures were then discontinued for three days and thereafter calcium chlorid was administered for five days; a slight diuresis occurred only on the second and third days of this therapy. When administration of calcium chlorid was started the patient was feeling quite comfortable and there was no apparent hydrothorax, ascites or edema of the extremities; crackling rales at both lung bases persisted however.

There were no apparent changes in the circulatory mechanism and the subjective symptoms were not noticeably changed by the calcium chloride therapy.

CASE XIII.—C. P., (Hospital No. 259245), male, aged fifty-seven years, laborer, since his illness with typhoid fever in 1917 had had shortness of breath on exertion and edema of the feet and legs which increased during the day and diminished over night. In September, 1923, he came to the out-patient cardiac clinic and was found to have arteriosclerotic heart disease with congestive failure (edema over both shins); the electrocardiogram showed sinoauricular bradycardia, the rate varying from 45 to 55 per minute. He was digitalized and continued to take a maintenance dose of 0.1 gm. and 0.2 gm. of digitalis leaf on alternate days. His symptoms and edema were somewhat diminished in severity but he returned in two weeks with persistent edema of both legs. Diuretin, 3 gm. per day for a week, was added to the digitalis therapy and this resulted in the entire disappearance of edema and the loss of 3.5 kilos of weight in one week. However he returned again the next week with a re-accumulation of edema of both legs and was taken into the hospital.

In this case calcium chlorid given together with digitalis at that time for 5 days was associated with but slight diuresis. There were no significant changes in rhythm or in vital capacity. In the electrocardiogram the *P-R* interval became lengthened, while the negative *T* wave in Lead II tended to become positive.

CASE XIV.—H. P., (Hospital No. 260405), male, aged twenty-one years, was first observed in May, 1920, when he was found to have

rheumatic heart disease, mitral stenosis and regurgitation, aortic regurgitation, and fibrinous pericarditis. During the next three years he continued a well-ordered convalescent existence, being greatly limited in his activity by marked shortness of breath on exertion. On several occasions after undue exertion he became very weak, with feet and legs swollen, and had to remain in bed. For the first four or five days of rest in bed he would continue to feel weak and orthopneic, passed very small amounts of urine and the swelling would increase; then on the fifth or sixth day he would suddenly begin to pass a great deal of urine, sometimes with frequency (every fifteen minutes). He took little digitalis (never more than 30 drops of tincture per day) during these periods.

In January, 1924, he came to the hospital again in a state of marked cardiac failure with general anasarca and orthopnea. In addition to the previous cardiac findings he also had auricular fibrillation. There was no evidence of nephritis.

During eight days of calcium chlorid therapy, and restricted low fluid intake, the amount of urine per day was about equal to the total fluid intake excepting on the eighth day, when more marked diuresis occurred. The slight diuresis during the first seven days can hardly be ascribed to the calcium chlorid therapy alone and it is more likely that the rest in bed and restricted low fluid intake were chiefly responsible. The patient did not improve symptomatically and edema seemed to increase. The heart rate became somewhat slower (probably from complete rest in bed), but it remained relatively rapid and the large apex-radial pulse deficit persisted. The change in the *T*-wave of Lead II from slightly diphasic to upright may be ascribed to elimination of the digitalis which he had taken before coming to the hospital. Because of the poor condition of the patient it was necessary to apply more orthodox measures for his relief and after digitalization and the administration of large doses of diuretin, a marked diuresis occurred, the apex-radial pulse deficit disappeared, edema gradually became reduced, he lost 10 kilograms in weight and there was a marked subjective improvement in symptoms.

The evidence in this case indicates that calcium chlorid has not a digitalis-like action in the treatment of auricular fibrillation with cardiac failure and edema.

CASE XV.—S. S., (Hospital No. 263703), female, aged sixty-two years, housewife, an obese, short, elderly woman, complained of dyspnea and palpitation on exertion, and nocturia (3 or 4 times), which she began to notice in February, 1924. Four months later she came to the hospital and was found to have hypertensive and arteriosclerotic heart disease with slight congestive failure (edema of feet and ascites) and general arteriosclerosis. Heart rhythm was normal. Renal functional tests (Schlayer concentration test,

chlorid excretion, and nonprotein nitrogen in the blood) did not suggest nephritis but were compatible with passive congestion and arteriosclerosis of the kidneys.

Calcium chlorid together with the maintenance dose of digitalis was given for five days; no diuresis occurred until the fifth day and then it ceased with the discontinuation of calcium chlorid therapy. While this slight temporary diuresis may have been caused by the calcium chlorid therapy we can draw no definite conclusions from the data in this case.

CASE XVI.—H. H., (Hospital No. 263735), male, aged fifty-nine years, janitor, an elderly obese man, had been suffering from dyspnea on exertion for about five years. His symptoms became greatly aggravated following pneumonia a year and a half before coming under our observation in June, 1924. For the last year he had been confined to bed because of marked swelling of the legs and abdomen, and orthopnea. Fluid had been oozing through the skin of his legs and this was followed by a very painful dermatitis. He also gave a history of typical attacks of angina pectoris. He was found to have hypertensive and arteriosclerotic heart disease, and marked congestive failure with general anasarca. Tests of kidney function were consistent with marked passive congestion of the kidneys, there being no data pointing to acute or chronic nephritis.

Neither diuretin, digitalis nor calcium chlorid had any significant diuretic effect on this patient. Neither digitalis nor calcium chlorid had any effect on blood pressure or on pulse rate. Edema increased and he grew steadily weaker and died of cardiac failure on the twentieth day of his stay in the hospital. The significant finding at autopsy was a large heart; the kidneys presented a typical appearance of chronic passive congestion without any evidence of acute or chronic nephritis.

CASE XVII —R. J. B., (Hospital No. 259681), male, aged forty years, seaman, had had "attacks of kidney trouble" during the past eight years, corresponding to acute and subacute nephritis; he was treated with salt-free, low-protein diet and rest in bed for periods varying from days to weeks. Dyspnea on exertion and nocturnal paroxysms of orthopnea had occurred only in the last two years. He had been in bed for six weeks before coming to the hospital, presenting evidence of hypertensive heart disease with congestive failure, chronic nephritis (nitrogen retention type) and a moderate degree of uremia. He was markedly orthopneic, both lower extremities and the sacral region were edematous, and moist crackling rales were heard at the bases of both lungs. True pulsus alternans was detected by the blood-pressure method; halving of the pulse rate occurred between 260 and 240 mm. of mercury, systolic pressure.

Treatment with salt-free, low-protein diet, diuretics, including calcium chlorid, and digitalis had no beneficial effect. In the fifth week of his stay in the hospital he developed erysipelas, uremia became more marked and he died two weeks after the onset of this infection. Permission for an autopsy was not granted.

In this case of edema resulting from cardiac failure and chronic nephritis, neither calcium chlorid together with a salt-free, low-protein diet nor digitalis caused diuresis; nor had these measures any discernible effect on the circulatory mechanism directly. The changes which occurred in the electrocardiographic curve during calcium chlorid administration are similar to those which were observed immediately before and after this therapy and therefore cannot be ascribed to it but were due more probably to the retention of toxic substances which caused the uremia. (See paper by Wood and White.)

Discussion. The above 9 cases include 5 in which diuresis occurred during calcium chlorid therapy. In 2 of these (1 with normal rhythm and the other with auricular fibrillation) it occurred in association with the beginning of the régime of rest in bed, and therefore the diuresis cannot be entirely attributed to the calcium chlorid although this drug may have had some influence. In the other 3 a slight transient diuresis occurred after all apparent edema had been reduced with other measures, namely rest alone in 1 case and with the addition of digitalis in the other 2. Of the remaining 4 cases, 1 with rheumatic heart disease, auricular fibrillation and anasarca failed to respond to calcium chlorid but digitalization and the administration of diuretin was followed by marked diuresis and by great improvement in the patient's condition. Two cases of cardiac failure without nephritis and 1 with nephritis and uremia did not respond to any medication, digitalis, diuretin, calcium chlorid, alone or in combination.

In none of these 9 cases was there any clinical evidence to indicate that calcium chlorid administered by mouth had any effect on the circulatory mechanism. The slowing of the heart rate in the 2 cases of auricular fibrillation may be accounted for by the rest in bed alone. The persistence of a large apex-radial pulse deficit in both of these cases and the fact that no diuresis or other beneficial effect occurred in the one with anasarca while digitalization and the administration of diuretin were followed by marked diuresis and general improvement indicate that calcium chlorid had not a digitalis-like action in cases with auricular fibrillation.

Effect of Calcium Chlorid in a Case of Tubercular Polyserositis.
CASE XVIII.—H. A. S., (Hospital No. 260418), female, aged fifty-five years, housewife, had polyserositis, pulmonary tuberculosis, cardiac enlargement and auricular flutter. Her illness began grad-

TABLE V.—EFFECT OF CALCIUM CHLORID AND OF DIGITALIS IN A CASE OF TUBERCULOUS POLYSEROSITIS AND AURICULAR FLUTTER WITH VARYING DEGREES OF BLOCK. (CASE XVIII).

Date, 1924.	Therapy.	Fluid intake, cc.	Urine, cc.	Body weight, kilos.	Pulse rate.	Blood pressure.		Vital capacity, cc. air.	Paracentesis. Electrocardiograms.
						Sys.	Dia.		
Jan. 4	Abdominal paracentesis, 5 liters. Auricular flutter; auricular rate, 260; 2:1 to 4:1 block; ventricular rate, 80 to 125; T wave in Lead II diphasic.
5	Calcium chlorid, 15.0 gm.	1400	600	37.3	108	600	Right thoracoparacentesis, 900 cc.
6	Calcium chlorid, 12.5 gm.	1900	900	...	100	
7	Calcium chlorid, 12.5 gm.	2400	700	...	100	120	85	
8	Calcium chlorid, 12.5 gm.	2100	600	41.3	90	600	
9	Calcium chlorid, 12.5 gm.	1800	300	41.5	80	Electrocardiogram same as on January 4, except ventricular rate, 100 to 125.
10	Calcium chlorid, 12.5 gm.	2000	500	41.5	120	650	
11	Calcium chlorid, 12.5 gm.	1800	400	...	110	110	80	750	
12	Calcium chlorid, 12.5 gm.	1600	500	...	120	
13	Calcium chlorid, 12.5 gm.	2100	600	...	110	
14	Calcium chlorid, 12.5 gm.	2100	600	...	110	
15	Calcium chlorid, 12.5 gm.	1800	750	...	120	
16	Calcium chlorid, 12.5 gm.	1300	650	...	100	
17	Digitalis, 0.6 gm.	2600	900	44.0	108	115	85	700	Electrocardiogram same as on January 4.
18	Digitalis, 0.1 gm.	2500	1000	...	122	Electrocardiogram same as on January 18.
19	Digitalis, 0.1 gm.	2250	800	...	118	750	
20	Digitalis, 0.1 gm.	1700	700	45.3	100	
21	Digitalis, 0.1 gm.	1200	600	...	90	120	80	Auricular fibrillation (coarse); ventricular rate, 90; inverted T wave in Lead II = - 0.2 mv.
22	No medication	1500	700	...	100	700	Abdominal paracentesis, 5 liters.
23	No medication	1500	600	...	90	
24	No medication	1500	650	...	110	115	80	

ually six years before entrance to the hospital on January 4, 1924; fluid accumulation in abdomen and chest had been progressive, requiring paracentesis several times. There was slight fever only. Hemoptysis had occurred two years previously.

On physical examination at the time of entrance to the hospital ward she was emaciated and showed signs of old tubercular processes at both apices, marked ascites, bilateral pleural effusion, enlargement of liver and of heart, and auricular flutter with auricular rate of 270 and ventricular rate varying from 80 to 130. Abdominal and thoracic paracentesis yielded much fluid (5000 cc. from former and 900 cc. from latter) with specific gravity of 1011 to 1015 and lymphocytic smear.

Calcium chlorid therapy was begun January 6, and continued for eleven days at a dose of 15 gm. the first day, 10 gm. the next four days and $7\frac{1}{2}$ gm. thereafter. It was absolutely without effect either on the ascites, pleural effusion, weight of patient, auricular flutter or electrocardiogram. (See Table V.) Fluid accumulated steadily in the serous cavities in spite of its use. On January 18 the calcium chlorid was discontinued and digitalis was begun and continued for three days. A reduction of the ventricular rate resulted without appreciable improvement in the patient's condition. Ascites reaccumulated.

This case of polyserositis showed no beneficial effect from calcium chlorid.

Effect of Calcium Chlorid in a Case of Hepatic Cirrhosis with Ascites.

CASE XIX. — F. H. S., (Hospital No. 261984), male, aged forty years, automobile mechanic, had alcoholic cirrhosis of the liver with marked ascites and jaundice. He died on the tenth day of his stay in the hospital following a severe hemorrhage from an esophageal varicose vein.

There was no diuretic effect from calcium chlorid. It is interesting that although there was no evidence suggestive of nephritis of either the chlorid or nitrogen-retention type, the urine output remained about the same during large or small fluid intake. Fluid reaccumulated after both abdominal paracenteses.

In this case of hepatic cirrhosis with ascites calcium chlorid affected neither the amount of ascites already present, the reaccumulation of ascitic fluid nor the elimination of urine.

Discussion. These 2 cases belong to the types in which Blum and his associates, and subsequently other authors, have observed beneficial results from calcium chlorid therapy. The administration of calcium chlorid had no apparent effect on the case of probable tuberculous effusion into serous cavities, nor on the patient with hepatic cirrhosis and marked ascites. In these cases also there was no evidence of any influence of calcium chlorid on the circulatory

mechanism; the auricular flutter in Case XVIII was not affected in any way.

TABLE VI.—CHANGES IN HEART RATE, RHYTHM AND ELECTROCARDIOGRAM DURING CALCIUM CHLORID THERAPY.

	Change.	Cases in which change occurred.
Rhythm	{ Normal to abnormal Abnormal to normal	None. None.
Rate	{ Increase Decrease	None. IV, X, XIV.
Extrasystoles	{ Newly produced or increased Decrease	None. IV.
<i>P</i> wave	{ Positive Negative	IV. None.
<i>P-R</i> interval	{ Lengthened Shortened	XIII, IV. XIII, IV.
<i>Q-R-S</i> complex, Lead II	{ Slurred or notched Widened	IV. None.
<i>T</i> wave, Lead II . . .	{ Positive Negative	I, IV, VI, XIII, XVII. I, V, VI, XIV, XVII.

Effect of Calcium Chlorid Administration on the Electrocardiogram.

In 11 cases electrocardiograms were taken before, during and after calcium chlorid therapy and some change or other was noted in 8. In no case did any change in rhythm occur and the variations that were observed were not uniform. In 3 cases there was a decrease in rate which, however, is to be attributed to the fact that this change occurred during the first part of the patient's stay in the hospital under a régime of constant rest in bed. In Case III a prolongation, then shortening, of the *P-R* interval and also an increase in positivity of the *T* wave in Lead II occurred during calcium chlorid therapy. In Cases I, VI, and XVII the *T* waves of Lead II varied in their changes from day to day, sometimes toward negativity and at other times toward positivity. Case XVII had uremia, and, as Wood and White have shown, such changes in the *T* wave occur in cases of nitrogen retention probably as a result of toxic effects on the myocardium. The electrocardiogram of Case XIV showed auricular fibrillation without any change in this rhythm but slight negativity of the *T* wave in Lead II. Case IV showed numerous changes, including prolongation of the *P-R* interval, increased positivity and notching of the *P* wave, increased negativity of the *T* wave and change from slurring to notching of the *R* wave in Lead II; in this case the frequency of extrasystoles and the heart rate were diminished only after marked diuresis had caused much improvement in the general condition of the patient. In view of the fact that in the other 18 cases the heart rate was not affected by calcium chlorid therapy, it is inferred that in this case the slowing of the heart rate was secondary to the effect of diuresis on the circulatory mechanism rather than that the

slowed heart rate was responsible for the diuresis. As regards the other changes it is probable that they were as likely due to sclerotic changes in heart muscle as to the direct effect of calcium chlorid upon the myocardium.

In view of the lack of uniformity of the changes and the simultaneous existence of other variable factors it is not possible to draw any absolute conclusions as to the effect of oral administration of calcium chlorid upon the electrocardiogram. It appears probable that there are no direct effects.

In Case IX electrocardiograms taken just before and immediately after the intravenous injection of 1.5 gm. of calcium chlorid showed no change as a result of this procedure.

Summary. The administration of large doses of calcium chlorid by mouth in two normal individuals was accompanied by a moderate temporary diuresis and no apparent significant changes in the circulatory mechanism as studied by clinical methods. Acidosis accompanied the diuresis.

Of the cases of heart disease with congestive failure and edema a group of 6 which had not responded well to treatment with rest in bed only, or together with digitalis and various diuretics, showed a well-marked diuresis during the administration of calcium chlorid. The diuresis began on the first to the fifth day of calcium chlorid therapy and in 3 cases did not cease until this drug had been discontinued for one or more days. In another group of 9 similar cases (excepting 1, XVII, who also had chronic nephritis and uremia) no significant diuresis occurred which could be attributed to calcium chlorid and in 3 of these digitalis alone or together with calcium chlorid or other diuretics also failed to cause diuresis. One case of this group (XIV), a patient with auricular fibrillation, after eight days of calcium chlorid therapy without beneficial effect responded readily and well to digitalization and the administration of diuretin.

In 2 miscellaneous cases, namely, 1 with probable tuberculous polyserositis and another of hepatic cirrhosis with marked ascites there was no diminution of the amount of fluid in the serous cavities nor was the continued accumulation of the fluid arrested by calcium chlorid therapy.

Data obtained upon heart rate, blood pressure, and vital capacity showed no evidence of direct effect of calcium chlorid administration upon the circulatory mechanism. Whereas some changes or other were noted in the electrocardiograms of 8 patients, there was no effect on rhythm or rate and the variations were not consistent either in different cases or in individual cases. Other variable factors, like recovery following previous digitalis therapy, uremia, improvement in circulation with marked diuresis from constant rest in bed, etc., were present in these cases and therefore it is not possible to draw any definite conclusions as to the effect of calcium chlorid.

therapy on the electrocardiogram. It is obvious however, that calcium chlorid has no digitalis-like action upon the heart. From this it may be inferred that the diuretic effect of calcium chlorid is due to its influence upon water metabolism in the tissues rather than upon the circulatory mechanism.

In no case did we observe any deleterious effects on the patient's condition as a result of calcium chlorid therapy.

Conclusions. 1. In cases of cardiac failure with edema in which constant rest in bed, digitalization, and the administration of various diuretics have not resulted in a satisfactory diuresis, calcium chlorid may be employed as a diuretic.

2. No deleterious effects were observed from the oral administration of calcium chlorid, 10 to 15 gm. per day, in any of the cases studied.

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THE VALUE OF VENESECTION IN THE TREATMENT OF THE DECOMPENSATED HEART.

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IN reviewing the early history of medicine, there is a striking periodicity of certain forms of treatment in disease. Some methods have been entirely empirical and their value and usage has depended largely upon the enthusiasm of the different observers. Such examples of therapeusis as cupping, blood-letting, balsams, baths, massage, metallic preparations and diets, as practised by early physicians have all repeatedly had their day of favor and decline through many centuries. One method, however, which has especially flourished and at times assumed an important role in the treatment of a rather wide field of disease is venesection. Although this method was held in universal esteem, there was never any agreement among practitioners as to the reasons for using it, the benefit derived from it or the technic. Hippocrates apparently used it with moderation. Galen, who loved to expound Hippocratic doctrines, wrote two treatises upon blood-letting. The Arabs introduced the theory of revulsion, which later stirred up the classic controversy between Brissot and the faculty at Paris. However, much these gentlemen may have quarreled among themselves concerning the theory underlying phlebotomy and the manner of administration, not one of them was heretical enough to discard it. It apparently never occurred to them to question the efficacy of the practice.

Yet having held sway for so long, it fell abruptly from its high estate during the middle of the nineteenth century. There seems to have occurred about 1850 a complete reversal of opinion among physicians and the general public which was the more remarkable because of the universal reliance upon blood-letting by a generation immediately preceding. From 1800 to 1840 there is a succession of papers which not only take the practice for granted but carry it to morbid lengths. Such examples of the freest possible use of leech and scalpel may be found in the works of Clutterbuck¹ and Wardrop.²

The feeling of resentment toward the practice of blood-letting in the seventeenth and eighteenth centuries and the deaths of several prominent men, such as Generals Washington and Harrison, naturally influenced the population in turning toward other methods of treatment. Until the time of Louis³ no careful analysis had ever been made with a view of determining the exact value of bleeding

in definite conditions, taking into account the factors involved in previous treatment, the severity of the attack, the age of the patient and so forth. Louis came to the conclusion that the reliance placed on blood-letting was not justifiable. In discarding venesection as a method of treatment, however, the pendulum swung too far in the opposite direction. Bowditch,⁴ about fifty years ago, realized this and in a paper in 1872, while deploring the evils of an earlier day, he mentioned a few cases which he had treated successfully by this method and believed that a rational use of venesection should be employed. For as he says it is recommended "in all acute cases where from any cause the heart apparently becomes distended with blood and consequently the circulation is greatly impeded, whereby orthopnea, lividity of the skin, with a very small and generally rapid pulse, mixed perhaps with other serious and disturbing symptoms, are produced."

It is difficult to estimate how often venesection is actually employed in general practice today, but its use in most hospitals may be said to be extremely limited. It has fallen away almost entirely in the treatment of infections and in certain diseases where the etiology was not previously known. In heart disease it is rarely used because of the satisfactory results obtained from such measures as rest in bed, theocin, digitalis, limitation of fluids, sedatives and so forth. However satisfactory the present treatment may be considered, the general disapproval and abandonment of venesection should not be unqualified in certain specific cases without critical study. That a certain well merited value in the treatment of the decompensated cardiac, for instance, has been overlooked and that actual revival may be in progress is suggested in a recent article by Christian⁵ on the treatment of heart disease. He states that in marked cyanosis and its attendant dyspnea bleeding is often of great value, and that it is "far too little used at present in the management of the decompensated cardiac."

It is a common experience in speaking with practitioners, accustomed to analyze critically results of therapy, to have them state that certain patients, during severe forms of circulatory embarrassment, have responded dramatically to venesection. They have also admitted their failures, and in studying the unsuccessfully treated patients, consider their failures were due largely to the improper selection of cases for venesection or to the imperfect understanding of the limitations to which the procedure is subject.

Unfortunately, it is difficult to analyze a large series of patients with failure of the circulation, who have been subjected to pure venesection without the addition of other measures of treatment and to compare them with a like series of heart cases given well recognized therapeutics. The reasons are obvious. For instance, many patients receive such treatment before admission to the clinic that deductions as to the effect of venesection alone would be impossible.

Simple rest often produces surprisingly good results, where no medication has been given. If venesection were performed on a patient who was just on the verge of passing into a period of improvement as a result of previously administered therapy, it would be difficult to evaluate the exact part played by bleeding in the recovery. In studying the heart, such complications as fluid in the chest or the abdomen or cloudy lung fields have no doubt interfered with determining such factors as change in size and shape during the illness.

There has been, however, a steady flow of experimental evidence on certain features of the circulation. As far back as 1830 John Reed,⁶ of Edinburgh, performed certain animal experiments which seemed to indicate an improvement in heart contractions after bleeding. Some attention has been given recently to the effect of bleeding on the size of the heart in animals. Eyster and Meek⁷ and others have reported a moderate contraction of the heart following the withdrawal of venous blood amounting to about 2 per cent of the body weight. Although these observations have been made on animals with apparently normal circulation, they serve to emphasize what may be accomplished in human beings with acute dilatation of the heart.

Grant,⁸ in some recent therapeutic studies in cardiac patients, found that the oxygen saturation of the venous blood was increased and the peripheral circulation improved after bleeding. The striking clinical improvement in some of his patients aroused our interest in the possibility of demonstrating any immediate corresponding change in the size of the heart by roentgen ray as occurred in animals following venesection.⁹ The problem was to determine what changes occurred in the size of the decompensated heart after venesection by roentgenography and to correlate if possible such changes, if they occurred, with certain clinical observations of the patient.

The technic employed was similar to that followed in a heart study by Cutler and Levine.¹⁰ Briefly it consisted in placing the patient in a special bed which allowed the taking of roentgenograms at frequent intervals without disturbing the patient. The small series charted was selected from a group of 31 patients. The uncharted cases are those of the ascites and effusion group in which accurate measurements of the heart were impossible.

In the accompanying chart it will be found that 4 cases (Nos. 21032, 23894, 21929, 21191) showed a diminution in the size of the heart within a few minutes after venesection. In 2 instances there was a further reduction of these dimensions some time later. This was accompanied by a corresponding immediate improvement in the condition of the patient, strikingly so in 2 patients (Nos. 21032 and 23894). In 2 other patients (Nos. 21139 and 21192) there was a slight reduction in the outline of the heart but so small

as to be considered within the limits of error and there was no accompanying clinical improvement. These patients were all decompensated cardiacs but were free from abdominal and thoracic fluid except 1 (No. 21192), who had a moderate amount, not sufficient, however, to interfere with the obtaining of satisfactory roentgenograms. All patients, with the exception of 1 (No. 23894), who showed signs of serious heart failure, had spent a considerable time in bed and had been given various therapeutic measures before venesection was resorted to. In addition to this series there were 2 patients, 1 with hypertension and the other with hypertension and polycythemia, on whom venesection was performed. Although

ROENTGEN-RAY MEASUREMENTS OF THE HEART.

Hospital number.	Age.	Diagnosis.	Amount of blood withdrawn.	Time elapsed between venesection and taking of roentgenograms.	Transverse diameter of heart.	Immediate clinical result from venesection.
21191 . .	71	Chronic myocarditis, auricular fibrillation	550 cc.	A. . . B. 10 min. C. 30 min. D. 50 min.	17.4 17.5 16.6 16.1	Improved
21139 . .	23	Chronic cardiac valvular disease	500 cc.	A. . . B. 20 min. C. 55 min.	18.6 18.8 18.4	Unimproved
21929 . .	60	Chronic myocarditis, auricular fibrillation	600 cc.	A. . . B. 48 min.	18.2 17.2	Improved
21192 . .	44	Chronic cardiac valvular disease, auricular fibrillation, chronic passive congestion of the liver, ascites	500 cc.	A. . . B. 40 min.	15.4 15.0	Unimproved
23894 . .	58	Chronic myocarditis, arteriosclerosis	900 cc.	A. . . B. 20 min. C. 90 min.	20.9 19.6 18.8	Greatly improved
21032 . .	80	Chronic myocarditis	500 cc.	A. . . B. 45 min. C. 90 min.	18.5 17.6 16.2	Greatly improved
21364 . .	51	Hypertension	550 cc.	A. . . B. 45 min.	13.0 12.5	Improved
21448 . .	62	Polycythemia, hypertension	550 cc.	A. . . B. 28 min. C. 2 hours.	16.4 16.8 16.6	Improved
W. W. . .	24	Normal	450 cc.	Control 20 min.	11.5 11.5	Unchanged
S. C. . .	23	Normal	500 cc.	Control 18 min.	14.3 14.4	Unchanged
F. M. . .	26	Normal	450 cc.	Control 35 min.	16.5 16.3	Unchanged
D. W. . .	35	Normal	550 cc.	Control 25 min.	13.4 13.2	Unchanged

A. = Roentgenogram taken before venesection.

B. and C. = Roentgenograms made following venesection.

here there was definite clinical improvement, the heart did not diminish in size. Four other patients, who were normal individuals so far as known and who were bled as donors for transfusion, also showed no change in the heart. In studying this group due consideration was given to the position of the diaphragm as suggested by Williamson,¹¹ Bordet¹² and others. In all instances the measurements of both the chest and diaphragms corresponded in the films of the same individual.

This series, although necessarily small because of the difficulty of studying patients severely ill and of obtaining satisfactory roentgenograms, suggests that in some cases a diminution in the size of the decompensated heart occurs a short time after venesection with an accompanying striking clinical improvement of the patient. Just what physiological adjustment develops in the failing heart as a result of phlebotomy is open to speculation. It may be assumed that because either a considerable load has been removed from the circulation or the viscosity has been reduced by the transfer of fluid from the tissues, the heart is able to more easily perform a function within its capacity, and thus develop an improved muscle tone. It would seem therefore that a failing heart becomes more efficient when extreme dilatation is reduced to a moderate dilatation. Cases which showed no improvement may come in the group of individuals with hearts so physiologically unresponsive except to the demands of the body at almost complete rest that tonicity and the powers of recuperation may be considered as practically negligible. The possibility that actual fatigue may be playing a part in dilatation is suggested by the fatigue which develops in the voluntary muscle with an insufficient blood supply. Wearn¹³ has reported some preliminary studies on the diseased hearts of adults which suggests that during dilatation there is a decrease of the blood flow through the capillaries of the heart. If this be true, it is possible that undernutrition and certain anatomical alterations develop various toxic substances in the myocardium which are improperly removed, and cause these hearts to be unresponsive to venesection. As Hewlett¹⁴ remarks, "the heart muscle may have become fixed in the new position so that even though strain be relieved or the muscle weakness disappear, the ventricle remains permanently larger than before."

The explanation for the absence of the diminution in heart size in the hypertension cases was probably due to either an insufficient amount of blood being withdrawn or to the absence of dilatation other than what was physiological. The same reasons may also explain the failure of obtaining a change in the heart in the normal individuals.

In order to get some idea of the feeling of house officers on the value of bleeding a number of records extending from 1914 to 1924 were reviewed. The impression received from the history notes is for

the most part enthusiastic about the immediate temporary improvement. Not a few notes suggest that the patient's life was actually saved by the procedure. In others there is a feeling of skepticism which suggests that bleeding accomplished no more than other less bothersome methods would have done. This latter sentiment is mentioned occasionally between many periods when venesection was quite freely used. How much this was due to the actual feeling that bleeding could be easily dispensed with or how often the proper subject for bleeding was admitted to the clinic was impossible to decide but there is a striking similarity to the periodic waves of bleeding that occurred in past centuries. In the hospital records, however, there is no evidence that blood-letting was employed to any great extent except on the decompensated cardiac, the hypertensive and occasionally in pneumonia. Quite satisfactory results from a purely symptomatic standpoint have been obtained in the hypertensive patients. The headaches, throbbing, dizziness have frequently been removed with striking rapidity although there has been only a slight temporary lowering of the blood pressure. A number of the decompensated heart patients have also received great symptomatic improvement, especially those with dyspnea, cough, restlessness, and the appearance of suffocation and cyanosis. Pulmonary edema is mentioned as being relieved considerably after venesection. Although relief in the cardiac group has not always been prolonged, it has, however, in many instances, been sufficient to carry the patient along while other measures were brought into play. There is one point which seems to be emphasized not infrequently in the history notes, and that is, where no beneficial effect was obtained from venesection, other procedures have also failed including the use of cardiac drugs and general stimulants.

The following cases are examples which serve to illustrate the immediate effect of venesection. They were taken from house-officers notes and are a part of the patients' record while in the Peter Bent Brigham Hospital. M. C., Med. No. 4303, male, aged thirty years. Diagnosis: Chronic myocarditis, chronic valvular heart disease and chronic nephritis. The patient had been in the hospital for several days under treatment. A note by Dr. S. A. Levine reads as follows: "The patient had considerable pain under the right costal margin evidently from a distended liver. He was bled 800 cc. which gave him considerable relief. Just before bleeding the edge of the liver was easily palpable a hand's breadth below the costal margin. It was pulsating. A short while after the bleeding was completed the edge was about two fingers below the costal margin and it was not tender."

C. W., Med. No. 16706, female, aged forty-five years. Diagnosis: Chronic myocarditis, hypertension, peripheral arteriosclerosis, acute uremia. This patient had been in the hospital for one day

before the following note was written by Dr. E. S. Emery: "For the first twenty-four hours in the hospital the patient seemed to be doing fairly well. She was rather stuporous but had no complaint and remained quietly in bed. On the evening of the second day she suddenly complained of shortness of breath. She was breathing very rapidly and shallowly and was deeply cyanotic. The pulse was rapid and rather weak. She gave the appearance of a patient in acute decompensation. Morphine was given which quieted her but she became extremely cyanotic, respirations were rapid and the pulse could hardly be obtained at the wrist. A phlebotomy was done with the withdrawal of 900 cc. Whether due to the treatment or not, she improved rapidly after bleeding, the cyanosis disappeared, breathing became easier and slower and the patient said she felt much better."

F. W. C., Med. No. 24767, aged fifty-seven years. Diagnosis: Infarct of the heart, angina pectoris, hydrothorax. Admission ten days before venesection. A note by Dr. R. B. Wilson is as follows: "Tonight about 10 o'clock the patient became extremely dyspneic, pulse being rather feeble, skin cold and clammy and rather markedly cyanotic. Following the venipuncture the patient felt immediately very much improved, the cyanosis disappeared, the pulse improved, the skin became warm, perspiration disappeared and the patient went to sleep in about twenty minutes, apparently greatly improved as the result of the bleeding."

Summary. The roentgenographic examination of a series of decompensated hearts in patients with failing circulation showed a diminution in the size of the heart immediately after venesection. When this occurred, there was a corresponding improvement in the condition of the patient. It is suggested that the hearts in these cases are more efficient in a moderately dilated form than when extremely dilated. In those cases, where no changes in the heart size occurred, it is felt that the muscle tone was so unresponsive to venesection because of certain anatomical changes in the myocardium that no improvement occurred in the circulation. A survey of the hospital records shows that numerous patients, bled as an emergency measure after other procedures of therapy such as drugs had failed possibly because of their delayed action, responded favorably to venesection. It seems, therefore, that venesection has a place in improving the action of the decompensated heart and temporarily, at least in removing signs and symptoms of failure.

I wish to express my appreciation to Drs. Albert Wilmaers and Guy Wells and numerous house officers for their help in carrying out the study and to Dr. M. C. Sosman and Dr. E. S. Emery, Jr., for many helpful suggestions.

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MICROCYTOSIS IN HEMOLYTIC ICTERUS.

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IN 1898 hemolytic icterus was first established as a clinical entity by Hayem.¹ He stated that, aside from the types of chronic jaundice caused by obliteration of the bile duct or compression by tumor and by hypertrophic biliary sclerosis, there were other types of the disease that were but little understood. He then described 5 cases of icterus with very large spleens and a marked chronic anemia, the red cells varying in number from 2,493,000 to 632,000 per cu.mm., and he classified this variety as of a markedly hemolytic type (*une maladie fortement déglobulisante*) with crises of varying intensity and duration. Bile pigment was present in the blood serum, but not in the urine, and the itching and clay-colored feces, found in other types of icterus, were lacking. He proposed to name the disease "chronic infectious splenomegalic jaundice of a paroxysmal type."

In 1907, Chauffard,² after eight years of study and research, described some cases of familial hemolytic jaundice with microglobulia and a greatly weakened cellular resistance, as shown by

the fragility test. He observed that the average diameter of the red cells was between 5 and 6 microns and that polychromatophilia and granular degeneration of the red cells were present. In this type of icterus the liver merely plays a passive part, serving as an organ of reception, transformation and insufficient elimination of the superabundant products and it is the spleen in reality that plays the preponderant part in this disease. Chauffard regarded hemolytic jaundice as a "noli me tangere" for the surgeon.

In 1900, Otto Minkowski³ published his studies of hemolytic icterus describing it as "a hereditary disease characterized by chronic icterus with urobilinuria, splenomegaly and renal siderosis," and the disease showed an anomaly in the destruction of the blood pigment subordinate to a primitive lesion of the spleen.

This hemolytic jaundice appears to be due to an excessive fragility of the red corpuscles, which, on liberating the hemoglobin, furnish the material for the production of jaundice. Here the resistance of the red cells to hypotonic sodium chlorid solutions is lowered, while in obstructive jaundice, pernicious anemia and splenic anemia the resistance of the red cells is increased.

In this disease there is no obstruction of the bile passages, but the spleen becomes greatly enlarged and filled with red corpuscles. According to William J. Mayo⁴ the spleen in the adult, like other organs of the reticulo-endothelial system, has for one of its proper functions the destruction of deteriorated red cells. When the spleen is enlarged as from splenic anemia or hemolytic icterus, this destruction may become excessive and produce the chronic anemia, leading to death directly, or indirectly through intercurrent disease.

One characteristic anatomical feature of this disease, seen on examination of the stained blood film, is the great majority of microcytes among the red cells. Evidences of active attempts at regeneration are also seen, such as polychromatophilia, and nucleated red cells, most of them normoblasts.

Naegeli,⁵ in his 1923 edition of "Blutkrankheiten und Blutdiagnostik," in discussing hemolytic jaundice regards these microcytes as belonging to a peculiar type of red corpuscles, which is inherited. He concludes that these inherited microcytes indicate a distinct type of human species.

While these red cells appear abnormally small they show an apparent increase of the hemoglobin content in each cell, while in secondary anemias from tumors, nephritis and in hemorrhage, and in chlorosis where large numbers of microcytes are found, the cells are much paler than normal. In fact, it is evident that these cells show, by their increased hemoglobin content, an approach to an actual spherical form instead of the normal biconcave or cup-shaped disk form.

Meulengracht investigated Naegeli's theory of the relation of microcytosis and its heredity to hemolytic jaundice and found that

the blood type was transmitted only by members of the family having the disease, the children of those unaffected being normal in this respect.

The question in regard to this microcytosis is this: Is it simply a characteristic symptom of the anemia in hemolytic icterus influenced to a large extent by the condition of the spleen and disappearing after splenectomy, or is Naegeli's statement true that the microcytosis is an intrinsic feature of this disease? In case the latter be true, we must expect that splenectomy would not change this abnormality of the red cells.

During the past three years I have been studying the blood conditions before and after splenectomy in some of these cases of hemolytic icterus, and during the past year a more detailed research has been made of the microcytosis and a decrease and subsequent general disappearance of the microcytes has been observed.

One cannot make an accurate decision in regard to this question by mere visual inspection of the red cells in the stained film and therefore exact measurements have been made of the cells before and after splenectomy by the following method. A series of successive fields in each particular slide was projected on paper by means of an Edinger apparatus, with measurements of a micrometer scale projected at the same focus. Outline drawings were made of the red cells in each projected field. Each cell was numbered, and its measurements were taken with a small pair of dividers and compared with the projected micrometer scale, and by this method 200 cells in each slide were measured.

Three of these cases of hemolytic icterus occurred in the same family, the mother and two small boys being affected.

Case Reports. CASE I.—Mrs C. W., gave a negative family history for this disease. She first noticed intermittent attacks of jaundice after her first labor, with loss of appetite, distaste for food and occasional nausea, but no vomiting. She was admitted to the Fordham Hospital on March 10, 1922, poorly nourished in her general appearance, with pinched facies and greenish-yellow complexion. No blood transfusion was given.

On March 16, splenectomy was performed by Dr. E. R. Cunniffe, the condition having been diagnosed as Banti's disease. The patient made an excellent recovery and was discharged from the hospital on March 30. Her jaundice disappeared, her general physical condition improved and within six weeks she had gained 15 pounds.

Blood Counts. The first blood count taken on March 14, 1922, showed a moderate degree of anemia (Table I) with some microcytosis of the red cells. A count taken on May 6, about six weeks after splenectomy, showed some general improvement in the blood findings and two subsequent blood counts taken at the Fordham

Hospital on October 9, 1922, and January 19, 1924, showed improvement in the blood picture, especially the latter. On May 15, 1924, she came to the surgical clinic of the Post-Graduate Hospital and a complete blood count was taken. This, and a later one on January 3, 1925, showed a return to normal.

TABLE I.—COMPARISON OF BLOOD COUNTS TAKEN FROM MRS. C. W. (CASE I) PREVIOUS TO AND FOLLOWING SPLENECTOMY, SHOWING A RETURN TO A NORMAL BLOOD PICTURE.

	Red cells.	White cells.	Gms. Hgb.	Differential count (per cent).								Platelets.
				Pol.	S. L.	L. L.	Mon.	Tr.	Eos.	Bas.	Myc.	
3/14/1922 . . .	3,000,000	5,400	10.5									
3/16/1922 Splenectomy												
5/ 6/1922 . . .	4,060,000	9,400	10.5									
10/9/1922 . . .	4,000,000	18,400	14.6	78	22							
1/19/1924 . . .	4,900,000	10,000	16.3	68	6	22		1	1	1		
5/15/1924 . . .	4,304,000	7,200	13.4	60	18	14	2	2	1	1		
1/6/1925 . . .	4,392,000	8,200	13.8	57	10	18	7	3	4	1		

CELL LENGTH IN MICRONS.

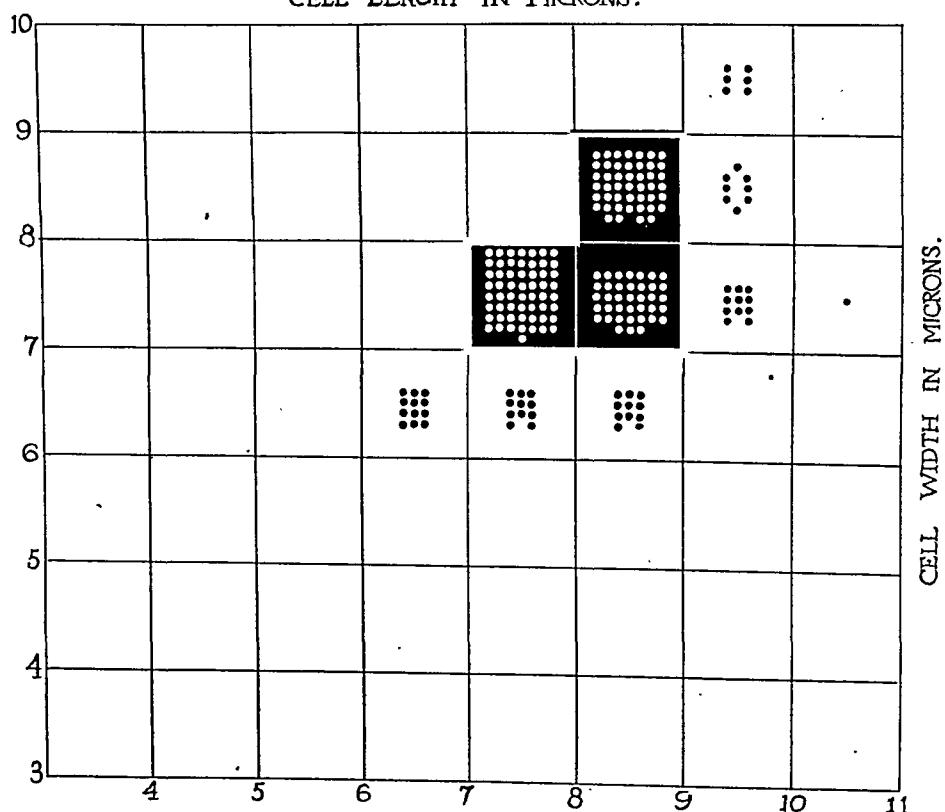


CHART I.—Measurements of 200 erythrocytes in a blood smear taken from Mrs. C. W. (Case I) two years and eight months after splenectomy. In this and the following charts the squares containing the cells of normal size (7 x 7, 7 x 8 and 8 x 8 microns) are bounded by heavier lines,

Microcytosis. No measurements were made of the patient's cells previous to her operation, but the cells in the smears taken on January 6, 1925, were measured and found to be quite normal in size (Chart I). For comparison measurements were made of the red cells in a smear of normal blood (Chart II).

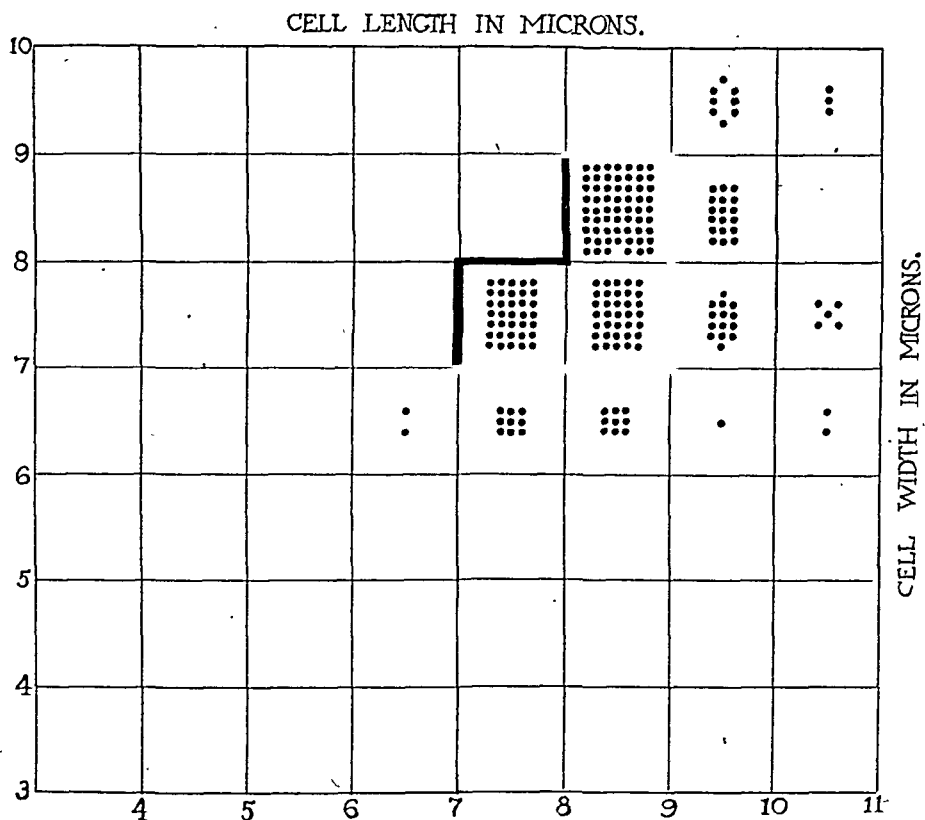


CHART II.—Measurements of 200 erythrocytes in a smear of normal adult blood.

CASE II.—R. W., older son of Mrs. C. W. (Case I), aged six years and two months, was born at full term, with normal labor, and was breast fed for ten months. He was very healthy until two and a half years of age, when he had an attack of jaundice. Since then, according to the mother, he always appeared yellow with marked pallor.

On February 16, 1924, he had an attack of vomiting with headache and fever which lasted ten days, followed by lassitude and pallor, and on February 28 he had another similar attack followed by increasing weakness and cramp-like abdominal pains. On March 6 he was admitted to the Post-Graduate Hospital.

The physical examination showed a well developed and well nourished boy, with a yellow-tinged skin. The abdomen was not distended, but hypersensitive on palpation, and painful on percussion. The liver edge was palpable just below the costal margin and the spleen palpable for two finger breadths below.

The Wassermann test was negative.

TABLE II.—COMPARISON OF BLOOD COUNTS TAKEN FROM R. W. (CASE II) BEFORE AND AFTER SPLENECTOMY, SHOWING A RETURN TO A MORE NORMAL BLOOD PICTURE FOLLOWING THE OPERATION.

	Red cells.	White cells.	Gms. Hgb.	Differential count (per cent).								Platelets.
				Pol.	S. L.	L. L.	Mon.	Tr.	Eos.	Bas.	Mye.	
3/ 6/1924 . . .	1,034,000	8,000	3.4	83	3	8	3	2			1	153,000
3/12/1924 Transfusion, 500 cc.	3,200,000	5,000	8.9	59	16	11	4	5	4			
3/18/1924 . . .	3,200,000	5,000	8.9	59	16	11	4	5	4			
3/20/1924 . . .	3,488,000	6,400	8.5	70	10	9	4	4	2	1		
3/21/1924 Splenectomy	3,408,000	5,000	10.4	50	19	10	16	1	4			
3/28/1924 . . .	3,408,000	5,000	10.4	50	19	10	16	1	4			
5/15/1924 . . .	4,190,000	7,000	10.5	50	30	10	7	1	1	1		
1/6/1925 . . .	4,384,000	8,200	12.9	52	31	11	4		2			

Blood Counts. The first blood count taken on admission showed a marked anemia (Table II) with polychromatophilia and granular degeneration. During the differential count 3 normoblasts and 3 microblasts were found. On March 12, the patient was transfused with 500 cc. of blood, and a count taken on March 18 showed a great improvement, especially in the number of red cells and amount of hemoglobin.

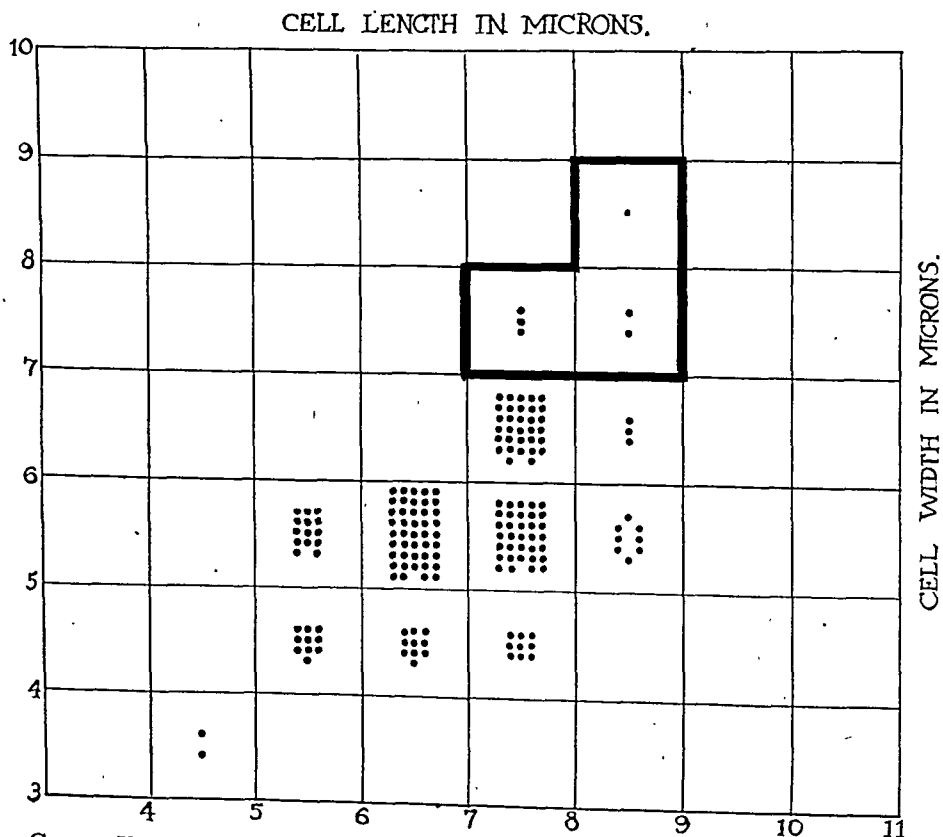


CHART III.—Measurements of 200 erythrocytes in a blood smear of R. W. (Case II) taken at time of admission to the Hospital on March 6, 1924. Note the small number of normocytes.

Splenectomy was performed on March 21 by Dr. J. F. Erdmann from which the patient made an excellent recovery, and on April 13 he was discharged.

The first blood count taken after the operation showed but little change in the cell count from that of March 20, but another count taken on May 15, when he was brought to the surgical clinic, showed a return to a more normal blood picture.

He was seen again on January 6, 1925, and was found to be in excellent general health, having had no illness since his discharge and he showed a healthy rosy color. The blood count showed quite a normal picture.

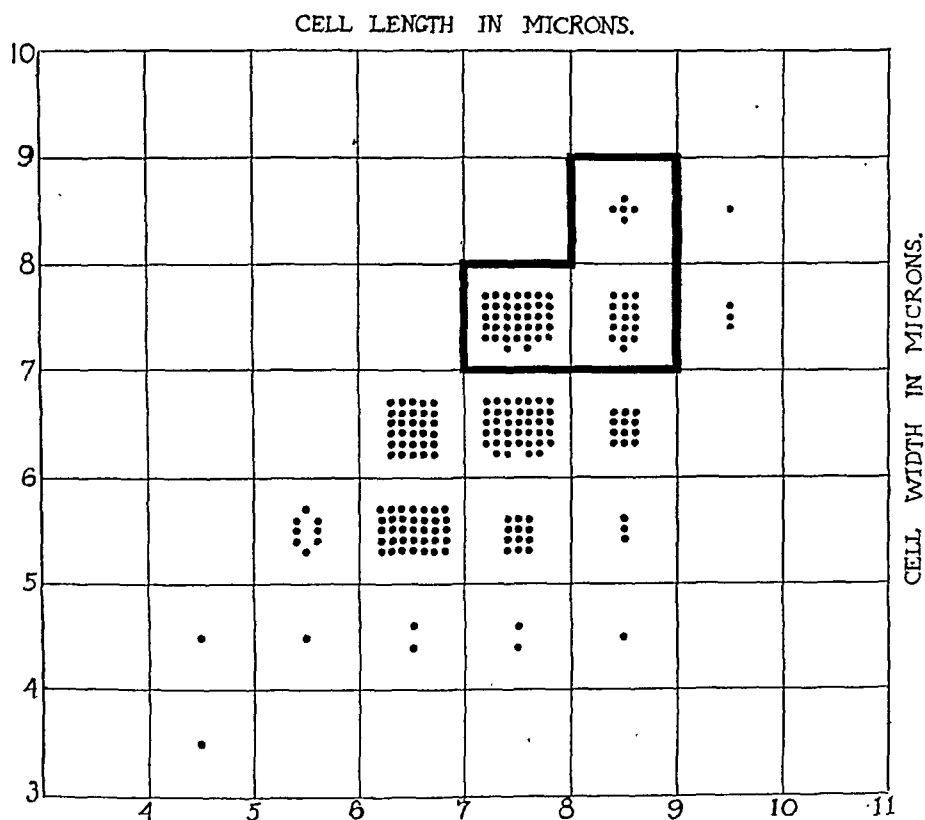


CHART IV.—Measurements of 200 erythrocytes from Case II in a smear taken on March 20, after transfusion.

Microcytosis. Measurements of the red cells in the smears taken on admission showed the majority of the cells to be microcytic (Chart III). After transfusion there was a moderate increase of normocytes, although the microcytes were still in the majority (Chart IV). After splenectomy, the measurements of the cells in the smears of March 28 showed the normocytes to be in the majority and in the smears of January 6, 1925, the vast majority of the cells were of normal size, and the microcytes very few in number (Chart VI).

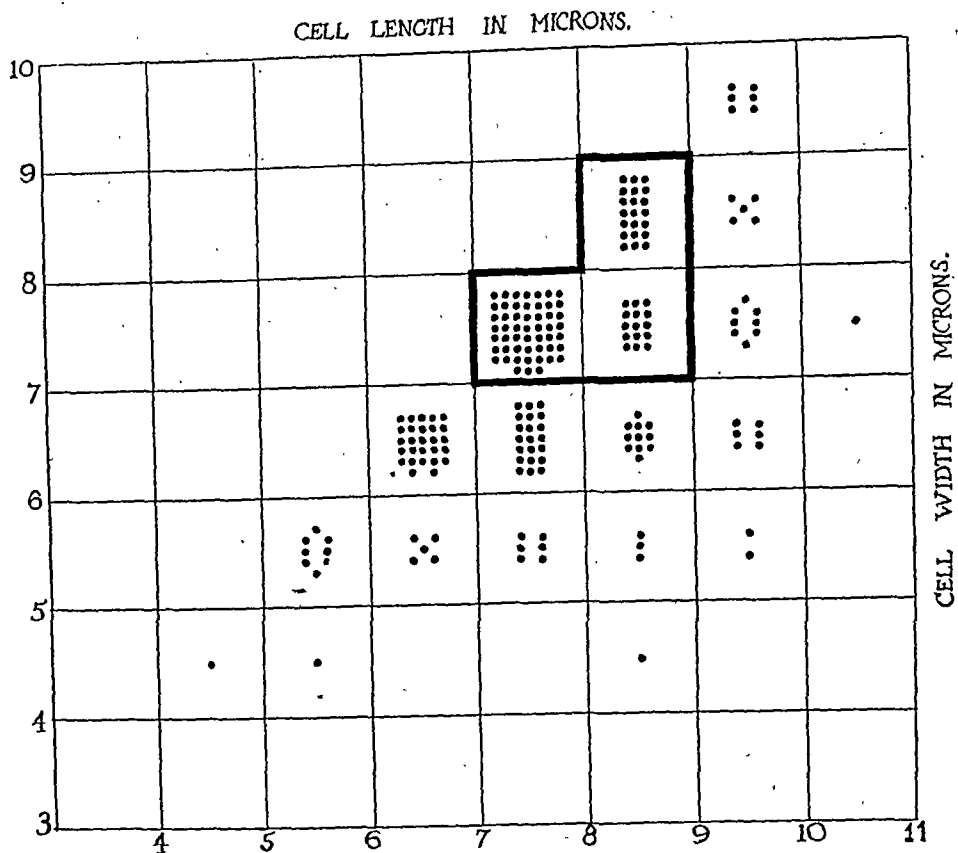


CHART V.—Measurements of 200 erythrocytes from Case II, in a smear taken a week after splenectomy, showing a return of the cells to a more normal size.

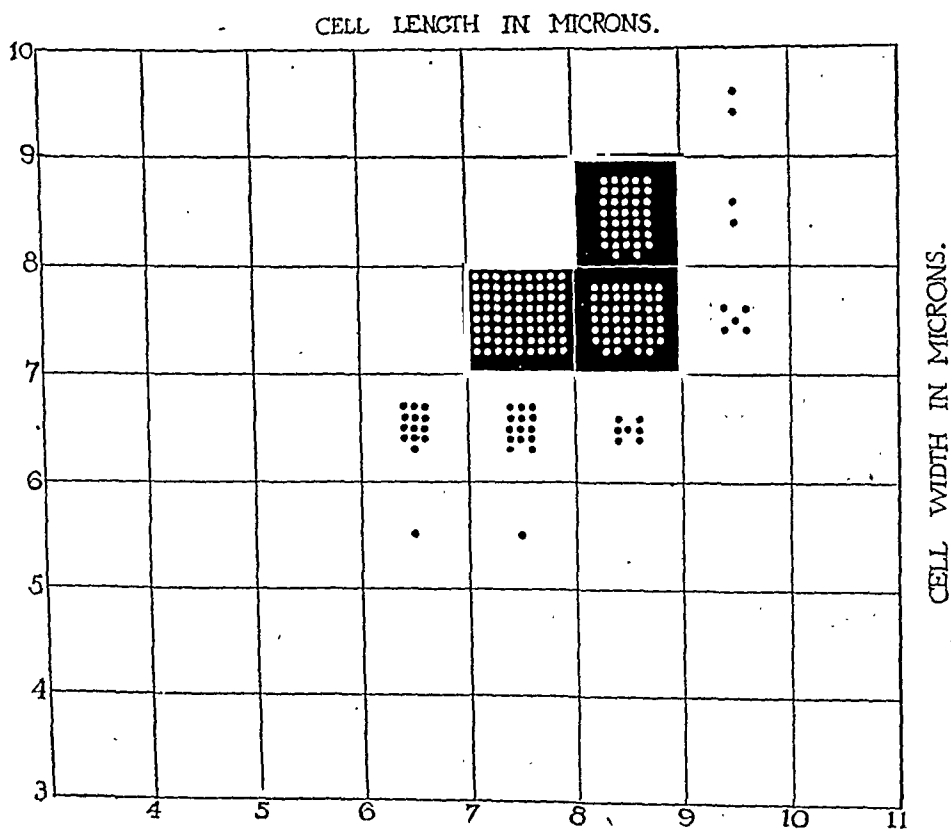


CHART VI.—Measurements of 200 erythrocytes from Case II in a smear taken on January 6, 1925, showing the vast majority of cells as of normal size.

CASE III.—A. W., aged four years, brother of Case II, born with normal labor and breast fed in infancy. On March 9, 1924, he had two very severe vomiting spells and afterward developed a slight fever with increasing pallor. He was admitted to the Post-Graduate Hospital on March 17. On examination he was found to be well developed and well nourished with a pale and yellow-tinged complexion.

TABLE III.—COMPARISON OF BLOOD COUNTS TAKEN FROM A. W. (CASE III) BEFORE AND AFTER SPLENECTOMY SHOWING A RETURN TO A NORMAL BLOOD PICTURE FOLLOWING THE OPERATION.

	Red cells.	White cells.	Gms. Hgb.	Differential count (per cent).								Platelets.
				Pol.	S. L.	L. L.	Mon.	Tr.	Eos.	Bas.	Mye.	
3/17/1924	1,736,000	10,600	5.4	67	17	11		5				136,000
3/21/1924 Splenectomy												
3/29/1924	3,640,000	6,200	10.2	65	11	9	7	2	4	2		
5/15/1924	4,208,000	5,800	10.2	41	21	26	5	1		1		
1/6/1925	4,416,000	9,000	13.4	61	27	10	1		1			

Blood Counts. The blood count on admission showed a marked anemia with many polychromatophilic and stippled red cells (Table III). During the differential count 13 normoblasts, 6 microblasts and 6 macroblasts were seen. On March 19 he was transfused with 400 cc. of blood which nearly doubled the number of red cells and the amount of hemoglobin.

On March 21 a splenectomy was performed by Dr. Erdmann. A blood count on March 29 showed a general improvement in the blood findings. The patient made an uneventful recovery and on April 13 he was discharged. Two subsequent blood counts of May 15, 1924, and January 6, 1925, showed a return to a good normal blood picture.

Microcytosis. The measurements of the red cells in the smears taken on admission showed a marked degree of microcytosis (Chart VII) but not as great as in Case II. After splenectomy, in the smears of March 29, the greater part of the cells were of normal size and only a few were microcytic (Chart VIII). In the most recent films the red cells were shown to have returned to normal size (Chart IX).

Fragility Tests. In Cases II and III a fragility test prior to operation showed a lowered resistance of the red cells (Table IV). On May 5, 1924, and on January 10, 1925, fragility tests of both boys and the mother showed a return to a fairly normal cell resistance.

Dr. Taro Toyada,⁶ in studying the red cells in congenital icterus under Naegeli, discusses a microcytosis of varying intensity present in all cases of this disease. These microcytes have no della but appear

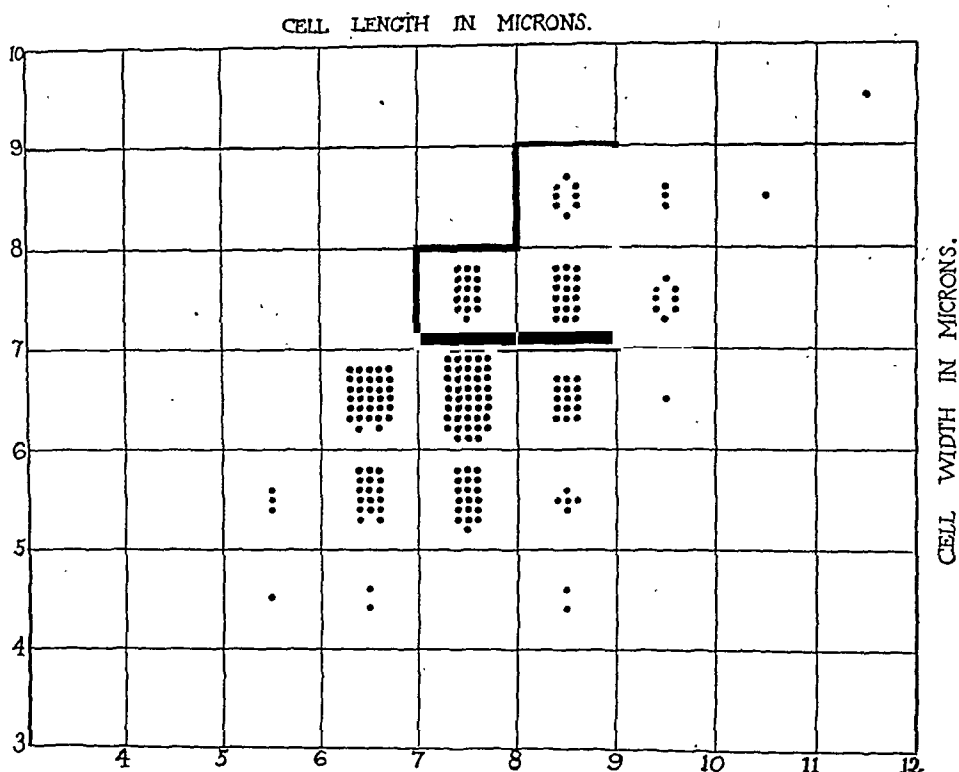


CHART VII.—Measurements of 200 erythrocytes in a blood smear of A. W. (Case III) taken at date of admission to hospital.

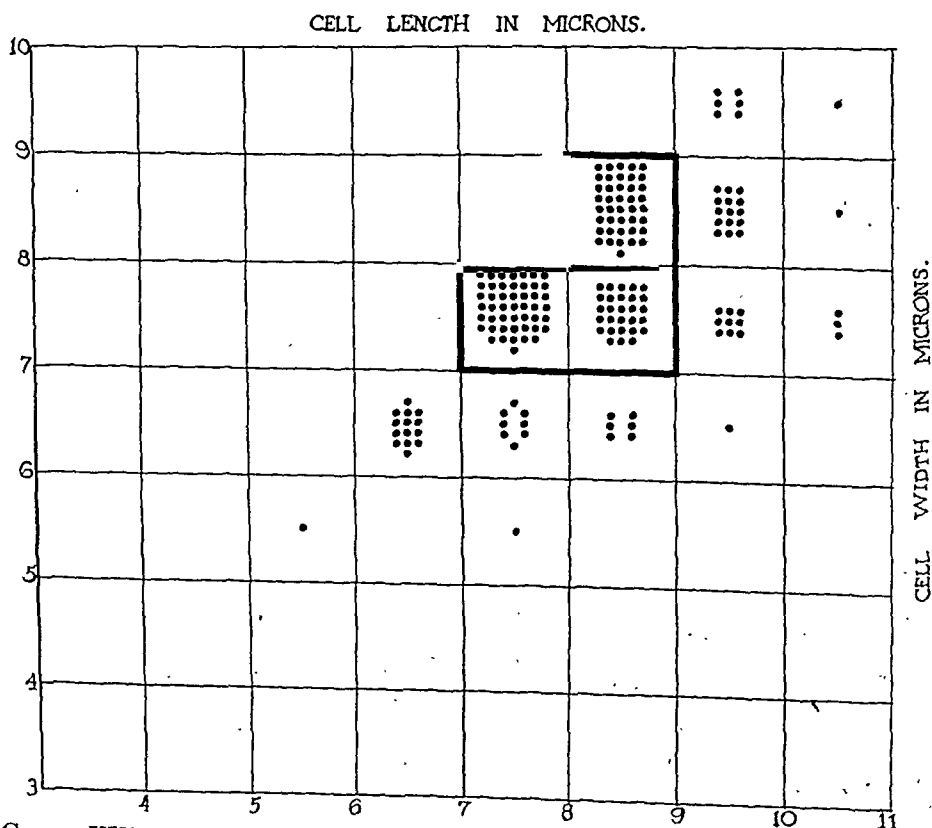


CHART VIII.—Measurements of 200 erythrocytes in a smear from Case III taken after splenectomy on March 29.

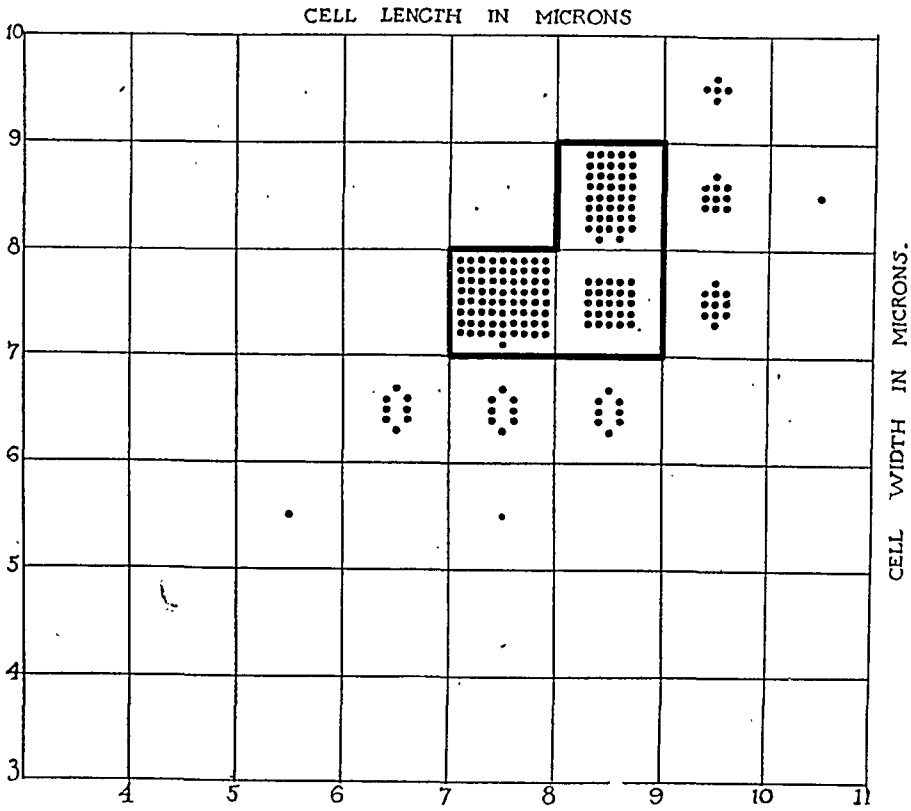


CHART IX.—Measurements of 200 erythrocytes in a smear from Case III taken on January 6, 1925, showing the greater part of the cells as normal in size.

REPORT ON TEST FOR FRAGILITY OF ERYTHROCYTES																			
Calculated percentage of Sodium Chloride	.855	.810	.765	.720	.675	.650	.585	.540	.495	.450	.405	.360	.315	.270	.225	.180	.155	.9	
Normal									I	—			C						
Case I. - Mrs. C.W.																			
May 15, 1924									I	—			C						
Jan. 10, 1925									I	—			C						
Case II. - R.W.																			
Mar. 18, 1924				I	—								C						
May 15, 1924									I	—				C					
Jan. 10, 1925												I	—				C		
Case III. - A. W.																			
Mar. 20, 1924				I	—								C						
May 15, 1924									I	—				C					
Jan. 10, 1925												I	—				C		

TABLE IV.—Comparison of fragility tests, in Case I after splenectomy and in Cases II and III before and after the operation as compared with a normal fragility test.

somewhat more intensely stained than normal cells, while cells 8 to 12 microns in size are usually pale and often polychromatophilic.

Toyada measured the red cells in a number of smears from patients with this disease and thereby found that in most of the splenectomized cases there was a marked decrease or total disappearance of the 4 and 5 micron cells, some decrease of those of 6 microns and an increase in those of normal size.

Summary. According to these studies of the blood pictures in hemolytic icterus before and after splenectomy, there is shown, from careful measurements of the red cells, to be a return to a more normal blood picture and a very distinct improvement in the corpuscles after the operation.

Therefore, because of the disappearance of the microcytes after splenectomy in contrast to their abundance in the blood in hemolytic icterus before the operation, this feature may be regarded as a concomitant manifestation of the anemia of the disease, rather than an inherent character of the erythrocytes of the individual.

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THE MAGNESIUM AND CALCIUM CONTENT OF THE BLOOD AND BLOOD PLASMA OF TUBERCULOUS PATIENTS.*

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THIS paper contains some observations regarding the magnesium content of the blood of normal people and people with pulmonary tuberculosis; it also gives the calcium content of the blood.

The calcium content of the blood serum has been the subject of extensive investigations in recent years, not only in tuberculosis, but also in other pathological conditions. The reasons for pub-

* The author wishes to acknowledge much personal assistance from Dr. L. Dienes whose methods and modifications were used.

lishing this relatively small series are: That the results were obtained with a different method from that ordinarily used and because the magnesium content is given as well. The great stability of the calcium content of the blood serum, the relation of the calcium values in the blood to certain pathologic conditions and the influence of the parathyroid glands in regulating the calcium content of the blood seem to be well established. Although there is not sufficient material to give us much idea as to the significance of magnesium in the blood, even a small series obtained by reliable methods seem to be not without interest. The remarkable consistency of both the calcium and magnesium values point to the possibility that even small variations in the values in different individuals can be the sign of important constitutional characteristics. Our purpose was rather to collect material to characterize the tuberculous individuals, to see if it would be really possible to find constitutional characteristics of them, rather than to obtain more insight into the disease.

The question of the methods used in the analytical work is very important. For instance, the method of De Waard for the determination of calcium which has been used quite extensively in Europe is (according to the seemingly valid criticism of Hirth and Klotz¹) not appropriate even for approximate comparative determinations. The method used by us, both for the calcium and magnesium determinations, is one recently described by L. Dienes.² The determinations are made after ashing the organic material, and the method is equally well applicable to blood and serum. The accuracy of the method is high; the parallel determinations usually agree to $\frac{1}{1000}$ mg. Two modifications were made in the original procedure: (1) In the precipitation of iron and phosphorus the weighing of the tubes was discontinued and readings were made of the volume in graduated tubes instead (using a tube 9 to 10 mm. in diameter and a volume of 1.25 cc., the error does not exceed 1 to 2 per cent); (2) in the same way, in precipitating the calcium, the tube was weighed only after pipetting off the oxalate solution. The amount of the solution was determined by the volume.

The accuracy of the method was somewhat influenced by the first modification, but no constant error was made by it and the technic and calculations were simplified.

Both the calcium and magnesium determinations were made on the blood and blood plasma, the plasma being obtained by centrifuging the cooled blood. For controls the red blood cell residue was also analyzed which, together with the values obtained from the plasma, enables one to calculate the values for the whole blood.

In the table containing the results of our work there are given, in addition to the classification of cases, some data on the constitutional characteristics, such as age, stature, state of nutrition

TABLE I.

NORMAL CASES ALL IN GOOD HEALTH AND GOOD NUTRITION	Calcium milligrams in 1 cc.		Magnesium milligrams in 1 cc.	
	Blood.	Plasma.	Blood.	Plasma.
F. K., 23 years; tall, slender, 137 lbs.	0.053	0.093	0.032	0.020
F. L., 22 years, medium build, 145 lbs.	0.052	0.092	0.033	0.022
E. S., 28 years, very tall, 195 lbs.	0.050	0.093	0.031	0.018
Mrs. F., 25 years, fairly tall, 145 lbs.	0.057	0.095	0.030	0.020
J. F., 33 years, medium, 170 lbs.	0.055	0.096	0.032	0.021
L. D., 38 years, medium, 142 lbs.	0.050	0.089	0.032	0.018
Mrs. S., 43 years, short, 135 lbs.	0.051	0.086	0.033	0.019
R. F., 46 years, tall, 165 lbs.	0.044	0.088	0.033	0.024
Miss B., 45 years, tall, 150 lbs.	0.052	0.096	0.039	0.026
<i>TUBERCULOSIS CASES—Incipient</i>				
Mr. Y., 38 years, tall, slender, improving nutri- tion, 150 lbs, normal temperature, now appar- ently well	0.043	0.079	0.032	0.021
Mr. B., 38 years, tall, slender, improving nutri- tion, 148 lbs, normal temperature, now much improved	0.048	0.075	0.037	0.024
Mr. H., 30 years, medium height, improving nutri- tion, 125 lbs., normal temperature, now appar- ently well	0.046	0.084	0.037	0.022
Mrs. H., 29 years, short stature, nutrition good, 110 lbs., normal temperature, now apparently well	0.051	0.083	0.032	0.025
<i>Moderately Advanced</i>				
Mrs. D., 36 years, tall, slender; improving nutri- tion, 112 lbs., normal temperature, now im- proved	0.046	0.080	0.033	0.023
Mrs. M. D., 21 years, medium height, 133 lbs., nutrition good, massive empyema, right thorax drained, normal temperature, now apparently well	0.045	0.085	0.035	0.020
Mr. B., 37 years, tall, slender, 130 lbs., nutrition improving, normal temperature, now improved	0.039	0.074	0.036	0.025
Mr. T., 39 years, tall, slender, 141 lbs., nutrition improving, normal temperature, now improved	0.044	0.086	0.029	0.020
Miss H. L., 30 years, tall, slender, 103 lbs., nutri- tion poor, but improving; temperature 99°, now improved	0.047	0.080	0.031	0.023
Mrs. C., 28 years, tall, slender, 123 lbs., nutrition improving, normal temperature, now very much improved	0.052	0.095	0.032	0.021
Mr. S., 35 years, tall, stout, 171 lbs., nutrition good, normal temperature, now very much im- proved	0.048	0.097	0.029	0.021
<i>Advanced</i>				
Mrs. T., 24 years, tall, thin, 93 lbs., nutrition poor, temperature 99°+, now unchanged	0.048	0.082	0.039	0.025
Mr. C., 30 years, tall, thin, 138 lbs., nutrition poor, temperature 100° to 101°, now unimproved	0.053	0.077	0.033	0.020
Mrs. G., 41 years, medium height, 100 lbs., nutri- tion poor, temperature 99°, now unimproved	0.052	0.086	0.031	0.021
Mrs. M., 41 years, medium height, 128 lbs., nutri- tion fairly good, temperature 100° maximum, now improved	0.050	0.085	0.032	0.025

and weight. The calcium values in the normal cases are a little lower than are usually found with the Kramer and Tisdall method and are considerably less than those obtained by the method of De Waard, which gives values with human serum that are too high according to Hirth and Klotz. Our normal values are very close to those found by the method of Hirth and Klotz³ (0.086 to 0.105 mg. in the plasma), which method also ashes the organic material first. Our values in pathologic cases are decidedly less than found by other workers, but this may be caused by chance, as the series is small. We are not inclined to attribute much importance to our findings in the tuberculous cases until they are better controlled by the same method. The determinations of the normal cases were made in a distinct series at a different time.

The magnesium values in the normal cases are very similar to those published by Kramer and Tisdall,⁴ and Salvesen and Linder,⁵ using Kramer and Tisdall's method, and the values published by Briggs.⁶ They are also similar to those of Blum and Klotz,⁷ determined after ashing the blood plasma (0.023 to 0.027 mg. per cubic centimeter of plasma). The range of variations is quite considerable from 0.018 to 0.026 mg. per cubic centimeter of plasma and 0.031 to 0.036 mg. in the whole blood. The same range of variations was found in the tuberculous patients. With our small material it was impossible to find any connection between the constitutional appearance of the individuals examined or their pathologic condition and the amount of blood magnesium. But the considerably greater variability of the magnesium content of the blood as compared with the calcium content makes an extensive study of them desirable. As the red blood cells contain more magnesium than the plasma, the determination of the magnesium not only in the plasma but in the blood also is necessary.

In recent years Walbum⁸ has observed that the intravenous injection of different inorganic salts can raise considerably the antibody production; he has even reported experiments according to which the resistance of experimental animals infected with tubercle bacilli can be raised by the intravenous injection of manganese salts. Of the salts which are very effective in the raising of antibody production it is only the magnesium which occurs in large quantity in the blood (besides traces of manganese). According to the conception of Walbum, the action of the salts is catalytic, accelerating the formation of antibodies, or it may be a stimulus of the reticuloendothelial system by the colloidal precipitate which is formed by the intravenous injection of the salts. The chemical individuality of the precipitate has a decisive influence. This observation gives a new interest to the study of the magnesium and was partly the reason we have undertaken it.

Summary. In normal and tuberculous individuals a variation of the magnesium content of the blood plasma was found between 0.018 to 0.026 mg. per cubic centimeter and 0.031 to 0.038 mg. in the whole blood. No connection with the pathologic condition or the age, stature and body weight was found. The calcium values in the blood plasma of normal persons determined after ashing it proved similar to the values found by others, using a similar method, but were found considerably less in the blood plasma of tuberculous patients.

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THE NONTUBERCULOUS PULMONARY FIBROSES.

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SINCE the recent epidemics of influenza numerous articles have appeared on the subject of the subacute and chronic pulmonary infections of nontuberculous origin. The outstanding features of these papers are the lack of details as to the exact pathology and the indiscriminate use of the words "unresolved pneumonia," "chronic interstitial pneumonia" and "pulmonary fibrosis." It was hoped that further light could be thrown on these conditions from a pathologic standpoint, but unfortunately it is difficult to obtain material since these cases do not usually progress to a fatal issue.

The following classification will suggest the wide range for study provided by this subject but in this paper discussion will be limited to the first group, with brief remarks concerning the others under the differential diagnosis:

Types of Pulmonary Fibrosis. 1. Following the acute respiratory infections.

2. Tuberculosis.
3. Syphilitic.
4. Pneumokoniosis.
5. Following exposure to war gases.
6. Fungus infections.

The problem is an important one, both economically and medi-

cally, for by recognizing the etiology and preventing the contributory factors a large amount of the resulting disability can be eliminated. From the standpoint of the child, at which age the incidence of this disease is greatest, much time lost from school could be prevented. With a more careful differentiation of cases in the adult many would escape the stigma of being labeled tuberculous, to say nothing of the economic saving by keeping them out of sanatoria. That this latter factor is important may be seen from the following statistics. Rist,¹ in his clinic at the Laënnec Hospital, Paris, found 62 per cent of the cases referred to him as tuberculous to be suffering from nontuberculous diseases. Many had been treated for long periods of time as tuberculous. Funk² states that out of 1200 consecutive cases referred to the tuberculosis wards of the Jefferson Hospital, Philadelphia, 6 per cent were nontuberculous. Stivelman³ in an analysis of 1700 consecutive admissions to a tuberculous sanatorium found 176 suffering from nontuberculous infections. Of these, 12 had chronic interstitial pneumonia, 10 had bronchiectasis, 11 had nontuberculous lung disease not definitely classified but suggestive of fibrosis.

A review of the literature dates back to the article by Corrigan,⁴ in 1838, in which he laid emphasis on the nontuberculous nature of a case of fibrosis and described the process of formation of bronchiectatic cavities by the shrinkage of the interstitial fibrous tissue. He labeled the condition "cirrhosis of the lung" and was the first to call attention to the displacement of the heart and other organs of the mediastinum.

In 1894 the first extensive work appeared on the subject written by Clark, Hadley and Chaplin.⁵ This contains a complete bibliography up to that date, from which the following points were extracted. Ivergensen and Rokitsansky⁶ were the first to describe an interstitial inflammatory process and gave it the name of "interstitial pneumonia." Eustace Smith⁷ thought the process occurred in the interlobular tissue and in the alveoli as well. Clark, Hadley and Chaplin⁵ discuss the pathology in detail stating that it is both an interstitial and an intraalveolar process and therefore refuse to accept the term interstitial pneumonia. They compare a series of tuberculous and nontuberculous cases, emphasizing the good nutrition in the latter group, the absence of fever in association with a normal pulse rate, and a chronic cough and expectoration.

Jacobi⁸ in an article on interstitial pneumonia describes it as one of the three types of pneumonia occurring in infancy and childhood. He believes it may occur as a sequela of the other pneumonias or as an independent disease occurring then most frequently in the right upper lobe and running a protracted course with fever for weeks or even months. Recovery is rarely complete, induration and retraction of the pulmonary tissue with bronchiectasis being frequent complications. He considers it a pulmonary hyperplasia,

with secondary fibrosis. The bibliography contained in this paper gives references to the important articles up to 1903.

Miller⁹ reviews the literature up to 1917 and reports on a series of 22 cases seen, which he divides into 3 groups: (1) The subacute type; (2) subacute type with recurrences, and (3) the chronic type. In this classification and in the articles reviewed by him there are examples of cases which went on to complete recovery (that is, probably so called unresolved pneumonias) and others in which there was a continuance of physical signs and symptoms, and which had undoubtedly developed a permanent fibrosis and even bronchiectasis. However, there is no definite classification on an etiologic or pathologic basis. The bacteriologic reports given show a predominance of the following organisms, in the order of their frequency: *Pneumococcus*, Type IV; *B. influenzae* and *Streptococcus viridans*.

Lord¹⁰ states that in a study of 85 cases of bronchopneumonia with autopsy no relation could be made out between the causative organism and the persistence of pulmonary signs and symptoms.

Riesman¹¹ discusses a lobar form of bronchopneumonia of long duration, occurring in children and young adults which clears up without residue and without evidence of retraction. The course of the disease extends from weeks to several months. It is commonest in the second decade and seems to predominate in girls.

Recently Packard¹² has called attention to the predominance of pneumonias of mixed type in recent years. Those due to the streptococcus and *B. influenzae* are largely lobular and tend to have the inflammatory exudate organized rather than resolved. He notes also the frequent formation of many small abscesses. Signs of unresolved pneumonia occur most commonly, according to him, at the angle of the scapula.

Symmers and Hoffman¹³ call attention to the increased incidence of organizing or unresolved pneumonia "which is anatomically and clinically distinct from the chronic interstitial pneumonia of syphilis, tuberculosis and the like since the connective-tissue replacement is almost exclusively confined to the intraalveolar spaces." This condition occurs according to them in a certain proportion of all cases of lobar pneumonia.

Louis Hammon,¹⁴ in the section on Diseases of the Lungs in *Oxford Medicine*, divides chronic pulmonary inflammatory conditions into:

1. Pulmonary cirrhosis, induration or fibrosis.
2. Secondary chronic inflammatory disease.
3. Primary chronic inflammatory disease.

He then goes on to say "secondary chronic inflammatory disease of the lungs, or as it is often called, chronic pneumonia, is usually a step on the way to cirrhosis. Unresolved lobar pneumonia is the commonest cause . . . Bronchopneumonia may be followed by a similar train of events."

Frequent attention is called in the literature to the importance of upper respiratory infections as a contributory factor in the disease. Field¹⁵ states that the frequency of mouth breathing and chronic nasal disease in children increases the liability to bronchial disease. He believes another predisposing factor in childhood is the relatively large amount of loose connective tissue in the walls of the bronchi and alveoli which is easily invaded by the infecting organism. He found *B. influenzae* most common, with the streptococcus and staphylococcus next in order. He suggests that dilatation of the smaller bronchi occurs early in the disease, as shown by the tendency to paroxysmal cough with large amounts of sputum.

Dunham and Skavlem¹⁶ point out that in 389 cases sent to the radiographer as possible pulmonary tuberculosis 18 had unresolved basal bronchopneumonia. These they considered were secondary to the following infections: Influenza 10; infected antra 3; infected frontal sinus 1; infected ethmoids 4.

Pierson¹⁷ also notes the importance of chronic upper respiratory infections, generally sinusitis, in connection with chronic pulmonary disease.

Hebert,¹⁸ who says that nontuberculous fibrosis is the commonest chronic pulmonary disease of childhood, points out the early age at which the process starts. He places the onset usually in the second or third year, following whooping cough or measles with bronchopneumonia, but finds that clinically the condition is not diagnosed until the child is eight or nine years of age. In his experience (personal communication) the unresolved pneumonias differ from pulmonary fibrosis usually in history and clinical course. The former come in children, generally after influenzal pneumonia or in adults after lobar pneumonia. The latter come after the bronchopneumonias of childhood, usually complicating measles and whooping cough. This is a persistent thing, going on usually to bronchiectasis. The unresolved pneumonias lose their symptoms in four to six months and repeated roentgenographs over a year or two show a gradual clearing of the dense area.

Very little is offered in the literature concerning treatment. Miller⁹ advises a dry climate and the removal of all nasal sinus infections. For those who have gone on to bronchiectasis he advises drainage by the inverted posture.

Jacobi⁸ believed the iodids were of value in early cases in which the hyperplasia had not gone on to cirrhosis. He recommended treatment with the drug over long periods of time.

Pierson¹⁷ suggests more radical measures. For early cases within six months of the onset and before extensive fibrosis has developed he would advise artificial pneumothorax. For those which show rapid progressions of the fibrosis and have large bronchiectatic cavities he advises thoracoplasty. In support of these radical measures is the frequency with which cerebral abscess and other septic con-

ditions occur as a complication of bronchiectasis (see postmortem statistics).

The present study covers a series of 30 cases personally seen in the wards and outpatient departments of several London hospitals and sanatoria. It includes a review of 1000 consecutive postmortems at the City of London Hospital for Diseases of the Chest and 1000 at the Hospital for Sick Children, Great Ormond Street, in which is seen the low incidence of fibrotic lung conditions.

TABLE I.—REVIEW OF 2000 POSTMORTEMS.

Diagnosis.	City of London Hospital.	Hospital for sick children.	Total.
Pure fibrosis	0	1	1
Fibrosis plus bronchiectasis . . .	16	2	18
*Bronchiectasis	13	3	16
Tuberculous fibrosis	7	1	8
Tuberculous fibrosis with bronchiectasis	9	2	11
	<hr/> 45	<hr/> 9	<hr/> 54

* Three cases of bronchiectasis secondary to mediastinal tumors and aneurysm were omitted.

TABLE II.—COMPLICATIONS.

Diagnosis.	Fibrosis and Bronchiectasis.	Tuberculous fibrosis.
Bronchopneumonia	2	6
Lobar pneumonia	2	0
Cerebral abscess	4	0
Septic meningitis	1	0
Pericarditis	2	0
Pyopneumothorax	2	0
Empyema	4	3
Gangrene	3	0
Tuberculous peritonitis	0	1
Miliary tuberculosis	0	3
Total	<hr/> 20	<hr/> 13

Several interesting facts are brought out in these tables, the most important of which is that pure fibrosis without any accompanying bronchial dilatation is seldom seen in the postmortem room. Table II shows the high incidence of septic complications in the nontuberculous group.

In the 2 groups there was a total of 18 children, 10 of whom had nontuberculous fibrosis and 8 tuberculous fibrosis. Of those over fifteen years of age, 27 were nontuberculous and 10 tuberculous. In this connection it is interesting to quote Hebert¹⁸ who says: "In adults the relative frequency of the two types of fibrosis is reversed and only prolonged investigation can justify the diagnosis of nontuberculous fibrosis." This is not in accord with the post-mortem figures given above, but it is undoubtedly true clinically. The discrepancy may be accounted for by the fact that most of these children survive to adult life.

Pathological Findings. GROSS. At postmortem these cases show a contracted lung which is tough and cuts with more resistance than normal. Small sections from densely fibrotic areas do not float in water. The pleura is usually thickened and often the lung is bound down by old adhesions. The hilum glands are usually enlarged moderately but show no caseation. On section there is present in practically all cases a varying degree of bronchial dilatation, greatest at the bases and frequently associated with small abscess cavities. (Fig. 1.)

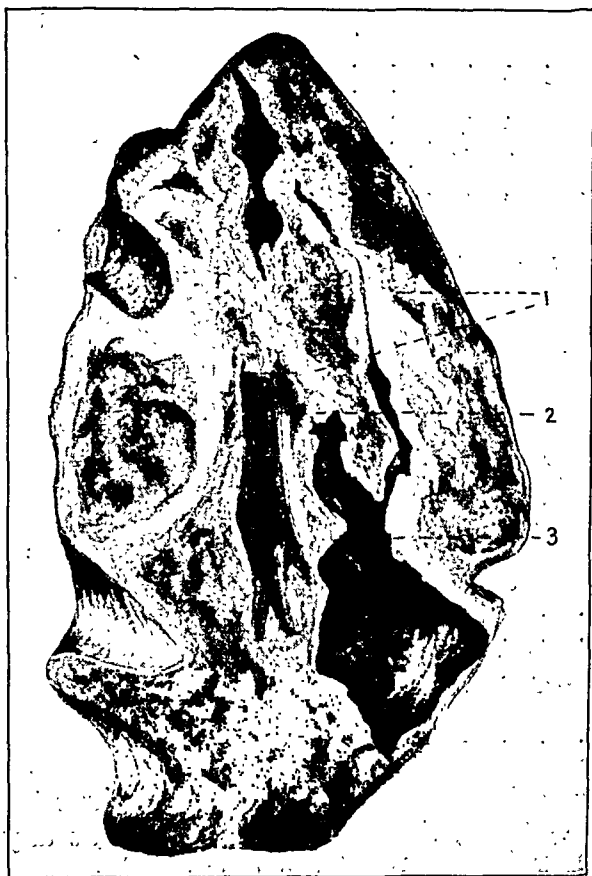


FIG. 1.—Section of fibrotic lung. 1, Fibrous tissue; 2, bronchus; 3, abscess cavity.

MICROSCOPIC. In the early stages there is an increased vascularity with the invasion of the tissues by lymphoid cells. Later one sees the development of elastic tissue fibers in the interalveolar spaces and around the bronchi and bloodvessels. Finally there is an obliteration of large areas of alveolar tissue, an absence of bloodvessels and the gradual contraction of the fibrous tissue. Coincident with this contraction there is a dilatation of the bronchioles and bronchi, due to the strain put upon their walls by the shrinkage of the adjacent tissue. Any inflammatory process going on in the

walls of the bronchi themselves undoubtedly aids this process. The columnar cells of the bronchial mucosa are often missing and there is a piling up of the cells of the basement membrane. (Fig. 2.)

It is regretted that no sections of early unresolved pneumonia could be obtained, but reference is again made to the article by Symmers and Hoffman¹³ who call attention to the fact that in these cases the process is intraalveolar and not interstitial, as in fibrosis.

ETIOLOGY. The frequency with which nontuberculous fibrosis occurs in childhood may be judged from the following fact: Out of 1000 consecutive admissions to the outpatient department at The Hospital for Sick Children, Great Ormond Street, 15 were diagnosed as having a nontuberculous fibrosis or unresolved pneumonia.

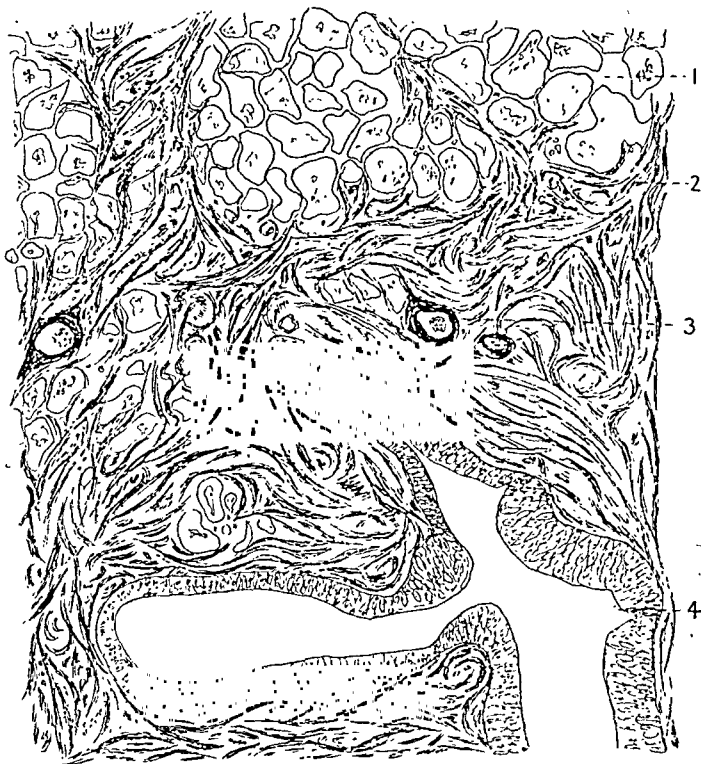


FIG. 2.—Section of fibrotic lung. $\times 1080$. 1, alveolar tissue; 2, fibrous tissue invading interalveolar space; 3, bloodvessels surrounded by dense fibrous tissue, 4, dilated bronchus.

In the 30 cases studied there were 20 children (between eighteen months and fourteen years of age) and 10 adults (ages nineteen to fifty-seven). In 14 of the 20 children the onset of the disease occurred during the first five years, the remainder between five and ten. In 7 the condition could be directly traced to a preceding whooping cough which was severe and usually associated with bronchopneumonia. Six dated their symptoms to pneumonia, of unknown etiology; and in 2 it followed a severe attack of chicken pox. Measles, although said to have aggravated a preëxisting

chronic bronchitis, was never given as the immediate precursor of the illness. In 5 children the exact relationship to previous infections was not known but in each case there was a history of repeated severe respiratory infections.

Among the adults the connection with preceding respiratory infections was equally definite. Of the 10 cases, pneumonia was the primary factor in 4. In 3 it was traced to influenza, in 2 the preliminary infection was undecided although there was a history in each case of repeated respiratory infections. One followed gassing with phosgene.

In all the cases there was a history of possible exposure to tuberculosis in only 4 cases.

SYMPTOMATOLOGY. The outstanding feature in all these cases was the recurrent cough, always worse in the winter. The children gave a constant history of loss of time at school but the adults were able to carry on with their work. The cough was productive, usually only with a fresh respiratory infection and often ceased entirely in the summer time. Those having the clinical signs and roentgen-ray evidence of bronchiectasis had a more copious expectoration but among the children the sputum was seldom foul and never in large amounts.

Dyspnea was more common in the adults but was never severe. Pain in the chest was not a common symptom. Eleven patients gave a history of night sweats. Hemoptysis and streaking of the sputum each occurred 4 times. Pulse and temperature were normal.

Among children in a healthy environment and with sufficient food (Cases I to IV) the general nutrition was good. But the average child coming to the outpatient department of the large hospitals was very much below par. They gave a history of wasting or of very irregular gain. They did well in convalescent homes but immediately lost on return to the city, and usually picked up a fresh infection.

Physical Findings. **APPEARANCE OF THE CHEST:** Contraction or flattening of the chest on the affected side is an important sign, occurring in 18 of the 30 cases. It usually involves the whole side of the chest and, when marked, is associated with scoliosis. Occasionally the flattening was limited to the supra- and infraclavicular spaces when the original process had been a localized unresolved lobar pneumonia. Diminished expansion, with poor air-entry on the affected side, usually occurs but is sometimes difficult to determine in children.

DISPLACEMENT OF THE MEDIASTINAL ORGANS. One expects to find with the process of shrinkage going on in the lung tissue, a displacement of the moveable viscera. Marked displacement of the heart is easily determined but where it is slight one is apt to overlook it. Confirmation with the roentgen ray is important. In the 30 cases displacement of the heart occurred 18 times. The

frequency with which displacement of the trachea occurs in tuberculous fibrosis is commonly used as a differential point (owing to the more frequent involvement of the apices) but in this series it occurred in 7 of the 23 cases rayed and considered to be nontuberculous.

PERCUSSION. The normal resonance of the chest is impaired on the affected side and is most marked, usually, in the lower two-thirds. In cases which have developed bronchiectatic cavities the dullness of course varies with the amount of retained secretion. Emphysema occurred in the adults but was seldom found in the children.

AUSCULTATION. These have been described by some writers as the "noisiest chests" one can listen to. But the sounds vary a great deal from time to time and, in fact, when no associated bronchiectasis is present the pure fibrotic chest often has diminished breath sounds with no rales. More often there is bronchovesicular breathing or a type of squeaky leathery breathing which is quite characteristic of marked fibrosis. Over dilated bronchi, tubular or amphoric sounds occur. Rales, when present, are large and moist and frequently have a metallic note. In the early unresolved pneumonias signs of consolidation are found, usually over a fairly circumscribed area. As the process clears the dullness, bronchial breathing and moist rales give place to moderate impairment, diminished breath sounds with a bronchovesicular character, and fewer rales. From this stage the findings depend upon whether the process undergoes complete resolution or progresses to fibrosis.

ROENTGEN RAY FINDINGS. The Roentgen ray findings show in most cases the following definite features: On the affected side the chest is contracted and by comparing the two sides of the plate one sees a diminished costochondral angle and narrow interspaces. With the fluoroscope, expiration is limited and the ribs on that side are seen to lag. The roentgen ray is particularly valuable in determining the presence and amount of mediastinal displacement which involves especially the heart but may also include the trachea and bronchi. In the lung fields the important points are a peribronchial thickening, extending particularly toward the bases, and a diffuse dilatation of the smaller bronchi which may be clearly seen as circular outlines varying in size from a millet seed to a pea. There is a varying degree of opacity present and emphysema may be seen in other parts of the lung.

VON PIRQUET. Since the need for diagnosis of these conditions comes largely during childhood the von Pirquet reaction is valuable. In the Vienna clinics a negative von Pirquet reaction is sufficient evidence to class a child as nontuberculous and this absolute reliance can be well understood when one sees how thoroughly the Viennese are able to check up their clinical findings by postmortem examination.

Lemon¹⁹ believes that flattening and immobility of the diaphragm are not sufficiently emphasized in the diagnosis of fibroid disease.

CLUBBING. Clubbing of the fingers is an important sign and should lead one to suspect bronchiectasis. In the 14 cases complicated by bronchiectasis it occurred in 6 children and 5 adults. In those who had no signs of bronchiectasis it was present in 2 children and 1 adult. It must not be forgotten that clubbing occurs in the toes as well as the fingers.

LABORATORY FINDINGS. It is regretted that owing to the variety of places from which this material was collected a greater uniformity of the routine laboratory work was impossible. The character of the sputum and a study of its bacteriology are important. As a rule the sputum, when present, is white and mucoid in contrast to the yellow or greenish purulent sputum of tuberculosis. In infancy, where sputum is not easily obtained, because it is swallowed, examination of the feces is advisable. A repeatedly negative sputum is good evidence that the condition is not tuberculous.

In those cases in which the sputum was cultured, the predominating organisms were the pneumococcus and streptococcus, which agrees with the statistics of other authors.

Course of the Disease and Prognosis. If one could definitely differentiate the more or less generalized process of fibrosis from the pneumonias with delayed resolution, it would be less difficult to picture the course of the disease. In general, one may say that the unresolved pneumonias show their maximum amount of clearing (best determined by the roentgen ray) within twelve to fifteen months after the onset. Any residue after this length of time is usually permanent and undergoes fibrosis. As a rule these cases become symptom free in four to six months after the acute illness.

Those patients having fibroid changes ultimately go on to bronchiectasis because of the shrinkage of the fibrous tissue and consequent dilatation of the bronchi. The relatively bad prognosis when this stage is reached may be seen from a study of the septic complications shown in the postmortem table. Probably few of those whose infection can be traced back to childhood live beyond forty-five years of age. Of the 35 nontuberculous fibroses obtained from the series of 2000 postmortems, 7 died in the first decade, 4 in the second, 5 in the third, 8 in the fourth and 11 in the fifth decade. The prognosis can be greatly influenced by the environment of the individual and freedom from fresh infections.

TREATMENT. In the treatment of the nontuberculous fibroses drugs are probably only palliative, although Jacobi's⁸ suggestion concerning the use of iodids is worth a thorough trial. In early cases breathing exercises are of definite value in helping to expand the chest, and the use of the Woulfe bottle is recommended.

Emphasis cannot be placed too strongly on the importance of a suitable environment in an equable climate, where they are free

from respiratory infections. It is particularly important to see that children are allowed to completely recover from their epidemic infections associated with bronchial involvement. The temptation to let children up, because of the difficulty in keeping them in bed, before the temperature and physical signs have returned to normal, undoubtedly plays its part in the development of these chronic lung conditions. All foci of infection, such as the tonsils, adenoids, and sinuses, should be thoroughly searched for and eradicated.

Pierson's¹⁷ views on the radical treatment of these cases has been gone into. It is of interest here to note that Davies²⁰ gives his mortality following thorocoplasty as 8.3 per cent and quotes Gravesen, and Jacobaeus and Key as having a mortality of 8.6 per cent and 8 per cent respectively. Brauer²¹ believes that with properly selected cases the mortality should not be over 2 per cent.

Differential Diagnosis. The separation of the nontuberculous from tuberculous fibroses is the most important problem in the differential diagnosis. A repeatedly negative sputum is the most valuable criterion but next in importance comes the history, dating back to a previous respiratory infection, the relatively mild character of the symptoms with a great tendency to recurrent cough. The pulse and temperature keep below the level usually found in tuberculosis and the amount of disability is not in proportion to the physical findings. The location of the lesion is important, for it is usually basal in the nontuberculous cases. In tuberculosis where there is a similar amount of basal involvement one will find at some time in the history of the case more marked constitutional symptoms, and the response to rest and improved hygiene is not so marked. The occurrence of hemoptysis does not necessarily point to the diagnosis of tuberculosis. It is produced by the erosion of vessel walls by secondary invading organisms and this can occur in either type of case.

The roentgen ray is a valuable adjunct. It is important to look for such evidence of tuberculosis as Ghon's "primary focus" which appears as a small calcified area usually well out in the lung fields, and the secondarily involved lymph glands which may or may not be calcified. The characteristic "fuzzy" opacities of tuberculosis are not seen. The presence of bronchial dilatation is in favor of fibrosis while true cavitation points to tuberculosis. The greater displacement of the upper mediastinal organs in the tuberculous type is again helpful but not conclusive, as shown by the cases given.

Clubbing may occur in both conditions but is more common in the nontuberculous fibroses which have gone on to bronchiectasis.

In childhood, use should be made of the von Pirquet test.

Case XXX is included in this series since it offers a difficult problem from the standpoint of the differential diagnosis. With the history of exposure to infection and other manifestations of

tuberculosis one feels justified in calling the lung lesion tuberculous. On the other hand, the excellent nutrition does not seem compatible with such an extensive tuberculous process in the lung. The presence of a positive von Pirquet reaction of the bovine type may help to explain the low toxicity of the process. Case XXXI is also interesting from the diagnostic standpoint. One would be inclined to discount the one and only positive sputum, found thirty-one years ago, and consider the case a nontuberculous fibrosis were it not for the great number of calcium deposits throughout the lung fields. This patient is further evidence of the greater disability and poorer nutrition occurring in the tuberculous type, in contrast to the nontuberculous. Simple chronic bronchitis can usually be differentiated by the fact that the signs are more widespread and the rales do not have the coarse, moist, consonating quality of a fibrosis.

The question will often arise as to whether one is dealing with an unresolved pneumonia or an empyema. Points in favor of the former are the absence of a septic temperature and sweating. The leukocyte count tends to be higher in empyema, although cases are seen in children in which a leukopenia persists. The roentgen-ray picture is more dense with fluid and with the fluoroscope one fails to get a clear space on deep inspiration below the opacity as one does with consolidation. By thorocentesis one should be able to settle the question.

The differentiation from a syphilitic fibrosis must depend primarily on the Wassermann reaction and the therapeutic test. Evidence of other syphilitic lesions is helpful. Funk² states that fibroid lesions of this character referred to syphilis do not possess any cardinal characteristics and cannot be distinguished during life from fibrosis due to tuberculosis and other causes.

Pneumokoniosis may proceed for years without giving any symptoms and may only be diagnosed when found by Roentgen ray or at autopsy. The more serious kinds such as silicosis, however, produce the physical signs of fibrosis and give rise in time to serious symptoms. The differential diagnosis depends on the history of exposure to dust inhalation, the diffuse nature of the lesions and the disproportionate amount of dyspnea with good general health. In the later stages the symptoms become more severe than in the type of nontuberculous fibrosis discussed in this paper. The Roentgen ray is of definite value in these cases since it shows the fine peppering throughout the lung fields with the inorganic particles.

That fungoid growths in the lungs may be a source of confusion in the diagnosis will be seen from the statement of Lord,²² in *Oxford Medicine*, to the effect that the thoracic form of actinomycosis is next in frequency to the abdominal type. He says "the abundance of connective-tissue formation is a striking feature and is responsible for the contraction of the affected side." The diagnosis here rests on finding the typical organisms in the sputum.

Case XXIX is included as an example of the difference between fibrosis subsequent to gassing and that following the respiratory infections. The excellent nutrition, marked dyspnea, sense of constriction in the chest and the fine tracery of the roentgen-ray shadow are all characteristic and in definite contrast to the other forms of fibrosis.

Case Reports. Following is a series of cases taken from the 30 studied, which illustrate the points brought out:

CASE XV.—Male, aged ten years. Diagnosis: Nontuberculous fibrosis; bronchiectasis. The family history is negative, with no known exposure to tuberculosis. The past history included left unresolved pneumonia at two years of age; measles at three; whooping cough at eight. The child has had a chronic cough since the pneumonia at two, and aggravated by whooping cough. Physical examination shows an undernourished child with clubbing of the fingers, which has been present since the age of two. There is slight contraction of the left chest but no displacement of the mediastinal organs. The percussion note is impaired throughout the left chest, especially at the base where there are harsh breath sounds and moist rales. The Roentgen ray shows marked fibrosis of the left chest with dilated bronchi. The sputum was repeatedly negative for tubercle bacilli, with the pneumococcus predominating. The pulse and temperature were normal.

CASE XVI.—Male, aged eighteen months. Diagnosis: Bilateral nontuberculous fibrosis; bronchiectasis. The family history is negative. Past history includes chicken pox at eight months, with persistent cough ever since, and wasting for the past three months. Physical examination shows an undernourished child with slight clubbing. There is a Harrison's groove and poor expansion of the chest. On percussion, there is impairment of resonance throughout both chests posteriorly and at the left base there are signs suggesting a cavity. The roentgen ray shows marked peribronchial thickening and dilatation of the bronchioles. There is no evidence of infiltration. The von Pirquet was negative. The sputum was negative 8 times for tubercle bacilli, with the streptococcus and pneumococcus being the predominating organisms. The pulse and temperature were normal.

CASE XXIX.—Male, aged thirty-seven years. Diagnosis: Gas fibrosis. The past history is essentially negative. The present illness began at the age of twenty-eight, when he was gassed with phosgene. Since then he has complained of tightness of the chest, dyspnea, cough and sweats. There is a small amount of sputum, which was streaked once. Physical examination shows an over-

weight man with slight cyanosis and no clubbing. The chest expansion is very poor. The percussion note is hyperresonant throughout and the breath sounds are bronchovesicular, with many musical rales. There is no displacement of the mediastinal organs. In the Roentgen ray the bronchioles appeared dense but fairly well defined, and there was a fine web-like tracery of diffuse fibrosis throughout both lung fields. The sputum was negative for tubercle bacilli 8 times. The pulse and temperature were normal.

CASE XXX.—Female, aged fifteen months. Diagnosis: Unresolved pneumonia; fibrosis; pulmonary tuberculosis. The patient's father died of pulmonary tuberculosis when the baby was two months old. The past history includes bronchopneumonia at five months, with fever for one month, lupus (?) at nine months, tuberculous dactylitis at fifteen months. The present history is that of chronic cough since the bronchopneumonia at five months. Physical examination shows a well-nourished child with slight contraction of the right chest. The percussion note is impaired over the entire right chest and the upper third of the left. The breath sounds are harsh over the left and distant on the right. There are no rales. A series of Roentgen rays showed gradual clearing of a pneumonic process in the right lung and upper third of the left, with the heart displaced to the left. There was questionable evidence of activity at the left apex. The sputum was negative for tubercle bacilli but the von Pirquet test gave a marked positive reaction with the bovine tuberculin. The pulse and temperature were normal.

CASE XXXI.—Female, aged seventy-one years. Diagnosis: Tuberculous fibrosis with excavation. The patient's father and one brother died of tuberculosis. The past history includes "inflammation" of the lungs at twenty-five and influenza at forty-six. She has had a chronic cough since she was twenty-five, with an hemoptysis at sixty-three and seventy. Her present symptoms are dyspnea, giddiness and weakness. Her sputum was positive for tubercle bacilli at the age of forty but has been repeatedly negative ever since. Physical examination shows the patient is very poorly nourished, with poor chest expansion and supra- and infraclavicular flattening. There is impaired resonance over the right upper and middle lobes, and to a less extent on the left. There are signs of a cavity at the right apex and crepitant rales and bronchial breathing at the left. The Roentgen ray showed masses of calcareous material throughout both lung fields, with signs of cavitation at the right apex. The pulse and temperature are normal.

Summary and Conclusions. An attempt has been made in this paper to bring out: (1) The salient points in the differentiation of

the nontuberculous fibroses; (2) the course and sequelæ of chronic pneumonic processes; (3) their prevention and treatment.

In the differential diagnosis the question of tuberculosis is of paramount importance. Here the history of the case, the general conditions of the patient, the von Pirquet reaction and Roentgen-ray picture are the determining factors.

The chronic pneumonic lesions of the lung can be divided from the clinical standpoint into 2 groups: one is the so-called unresolved pneumonia and the other chronic pulmonary fibrosis. Of the first, a certain proportion will entirely clear up in six months to a year while the others go on to a permanent fibrosis. But a large proportion of the group of pulmonary fibroses is made up of cases which have developed insidiously after whooping cough and bronchopneumonia without showing a definite stage in which one could say that resolution had failed to take place.

These primary infections occur usually in early childhood but the condition is not diagnosed until varying degrees of bronchiectasis have supervened.

Because of the long-standing disability, prophylaxis in these cases is exceedingly important. It can best be accomplished by removing sources of exposure to whooping cough and measles and, more particularly, by seeing that the lung has returned to normal after these infections before the child is discharged. When there is a residual lesion the case must be carefully followed by repeated Roentgen ray and physical examinations. In these cases it is especially important to remove all foci of infection both in the individual and his environment and to improve his general hygiene.

The treatment is largely palliative during the acute exacerbations. All sinus or throat infections should be carefully searched for and cleared up. In cases with extensive unilateral lesions and bronchiectasis, artificial pneumothorax, as advised by Pierson,¹⁷ has to be considered. Where collapse is impossible, owing to adhesions, one has to carefully weigh the seriousness of the symptoms and dangers from septic complications against the fairly high mortality attendant upon the more radical operations.

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A STUDY OF FOUR HUNDRED AND FIFTY CASES OF EPIDEMIC ENCEPHALITIS.*

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Introduction. The present outbreak of epidemic encephalitis seems to have started in Vienna in the winter of 1916 and 1917. Since that time an enormous literature has developed in continental Europe, England and the United States.

In this paper no effort will be made to review this literature, as our object is simply to present the outstanding features that have developed in the study of a rather large number of cases.

* Read before the University of Virginia Medical Alumni Society of New York City, May 22, 1925.

These cases were seen beginning in the fall of 1918 and during the following five years up to 1924. The 1924 cases, 81 in number, have not been included, as we wish to emphasize somewhat the after effects of encephalitis and it is still too early to report on the sequelæ of these cases.

In the fall of 1918 we first realized that we were beginning to see cases of a type that was new to us. Since 1910 the meningitis division has been studying cases of meningeal involvement, the different kinds of meningitis, poliomyelitis, meningism occurring in the various acute infections and other rarer conditions involving the central nervous system. This experience gave us a fairly good background on which to study this interesting disease.

At first we did not recognize that the cases were epidemic encephalitis. We were misled by the reports in the English literature, that the spinal fluid findings were negative, and also by the fact that the English reported that the cardinal symptoms were lethargy, asthenia and cranial nerve palsies. With rare exception, the spinal fluids in our cases have not been normal. While the triad of symptoms described by the English is very characteristic when present, many cases do not present all three and some not even one of these symptoms. As time has passed it has been recognized more and more that cases of epidemic encephalitis present a widely varied symptomatology. The term encephalitis lethargica seems to us very unfortunate, since it emphasizes a symptom which is frequently not present. It is very difficult to convince a patient or his family that he has encephalitis lethargica when insomnia and restlessness are the outstanding symptoms.

The following, Tables I, II and III, show the distribution of cases by year, season, sex and age:

TABLE I.—DISTRIBUTION BY YEARS AND SEASONS.

Year.	Jan. Feb. Mar.	Apr. May, June.	July, Aug. Sept.	Oct., Nov., Dec.	Total.
1918 . . .	0	0	1	10	11
1919 . . .	26	4	9	29	68
1920 . . .	65	19	11	16	111
1921 . . .	49	25	25	9	108
1922 . . .	18	34	8	11	71
1923 . . .	45	17	14	6	82
Total . .	203	99	68	81	451

From the above table it will be seen that the greater number of cases occur in the first three months of the year and the smallest number in the summer months.

TABLE II.—DISTRIBUTION AS TO SEX.

Year.	Male.	Female.
1918	5	6
1919	52	16
1920	68	43
1921	60	48
1922	34	37
1923	45	37
Total	264	187

From the above table will be seen that approximately 59 per cent are males and 41 per cent females, or a little less than a ratio of 3 to 2. The preponderance of males over females is slightly less than in epidemic meningitis and poliomyelitis. In these diseases about 50 per cent more males than females are attacked.

TABLE III.—AGE DISTRIBUTION.

Age.	1918.	1919.	1920.	1921.	1922.	1923.	Total.
Under 6 mos.	0	3	3	2	2	0	10
6 to 12 "	2	2	2	2	3	1	12
1 to 2 years	0	5	11	11	5	6	38
2 to 5 "	1	10	8	13	8	8	48
5 to 10 "	3	7	21	19	10	9	69
10 to 15 "	1	7	13	5	5	7	38
15 to 20 "	1	7	5	9	6	10	38
20 to 30 "	2	10	22	24	10	12	80
30 to 40 "	0	9	17	9	6	11	52
40 to 50 "	1	7	8	7	5	8	36
50 to 60 "	0	1	0	7	9	6	23
over 60 "	0	0	1	1	1	4	7
							451

It will be seen from Table III that of the 451 cases 234 were more than fifteen years of age and 217 cases were less than fifteen years of age. This is a larger proportion of cases in childhood than is reported by most workers. But we see an unusually large number of cases in children because many physicians in the city are accustomed to call us to help them in the diagnosis of meningeal conditions in children.

For some time we have felt that cases in children were frequently overlooked. If we have made an unusually large percentage of mistakes in the diagnosis of epidemic encephalitis in young children we have made it consistently. Up to the middle of May, 1921, when 274 cases had been studied they were equally divided between patients more than fifteen years of age and those younger.¹ Our findings are corroborated by the work of Happ and Mason,² whose age distribution of cases is almost the same as ours.

In contrast to this, about 65 per cent of cases of epidemic meningitis and about 90 per cent of cases of poliomyelitis are less than ten years of age.

Symptomatology. While the chief symptoms are those referable to the central nervous system, there are also symptoms, such as fever, which is usually low and irregular, vomiting and malaise, which may be caused by a general toxemia.

The onset is usually gradual but in a certain percentage of cases it may be abrupt. It is more likely to be sudden in children than in adults. The symptoms referable to the central nervous system are of the greatest possible variety and vary widely in the same patient during the course of the disease, which is often greatly prolonged. This indicates that we are dealing with a virus which may involve any part or combination of parts of the central nervous system and which may progress from one part to another during the illness. This is in marked contrast to the action of the virus in poliomyelitis which attacks suddenly and has usually progressed to the maximum within five to seven days. In poliomyelitis the action of the virus is far more selective, and the greatest damage is done to the cells of the motor area, especially to the cells of the anterior horns of the spinal cord.

We have made no attempt to divide our cases into groups. The multiplicity of symptoms necessitates so large a number of groups that the classification becomes too unwieldy for the use of the general practitioner. Moreover, on account of the progress of the disease the same patient would often fall into any one of several groups, depending on the time at which he was seen.

So much has been written on the symptomatology of epidemic encephalitis that our discussion will be brief. We do wish to emphasize the fact that quite often the symptoms are mild and in other instances different from those originally considered pathognomonic. We feel that the diagnosis is missed in many instances because the physicians are looking for lethargy, asthenia and cranial nerve palsies. While extreme lethargy and somnolence are very characteristic when present, a fairly large group of cases suffer from restlessness and insomnia. In some patients both somnolence and insomnia are present at different stages of the disease.

Ocular disturbances of various kinds are of frequent occurrence. Attacks of diplopia or blurring of vision are sometimes the earliest distinctive symptoms. These attacks may last for only a short time in the early stages or they may occur at intervals for a considerable period. Sometimes the diplopia or blurring is fairly continuous over most of the illness. Loss of vision, usually temporary, is occasionally seen. Other phenomena that are sometimes noted are: Ptosis, either unilateral or bilateral; strabismus, nystagmus and hippus. In one instance there occasionally took place

convulsive twitchings of the eyes which then snapped quickly to the left, and remained fixed for two or three minutes. These seizures occurred at frequent intervals during the height of the disease, but disappeared entirely as the patient recovered. In another case the eyeballs performed in succession a curious, nearly complete rotation, with the pupils looking inward. While one eye was in motion the other eye remained quiet, but there was more or less twitching of the lips and face muscles on the same side. While a large percentage of cases show a normal fundus, a slight haziness of the disc has been seen in a certain number of cases. Various degrees of optic neuritis with or without choking has been observed less often. Sometimes in late cases there is secondary optic atrophy.

In addition to the lethargy or excitability which are very common symptoms, and have already been referred to, delirium is not infrequently present. The delirium may last for a considerable time, or may occur at frequent intervals, lasting only for a few minutes. In other instances the patient is acutely maniacal for varying lengths of time. Catatonia is occasionally seen.

Sensory Disturbances. Headache is an almost constant symptom. Lancinating pains due to involvement of the posterior nerve roots are fairly common. These affect most commonly the arms and legs, but the thoracic muscles are sometimes involved. Numbness or tingling are less frequent symptoms. Occasionally there is loss of sensation, involving one or both legs and lower part of the trunk, resembling a hemitransverse or a transverse myelitis.

Trophic Disturbances. These are rare but do occur during the early or later stages of the disease. Repeated ulcerations of the cornea were seen in one patient beginning during the comparative early stages and lasting for several months. In another case there was an extensive furunculosis late in the disease, and in another case, also late, there were frequent attacks of stomatitis, thought to be trophic in origin. In one case the teeth decayed very badly after the attack of encephalitis and in another there was alopecia.

Motor Symptoms. One of the most striking of the motor symptoms which is found in a certain proportion of the cases is hypertonicity of the muscles. This is shown in the masklike expression of the face, in the general muscular rigidity and the slow movements. The rigidity of the neck due to this general hypertonicity must be sharply differentiated from the rigidity due to inflammation of the meninges. Muscular twitchings are a common phenomenon. They may be of several varieties. Myoclonic contractions may involve a single muscle or any group of muscles. Tetanic spasms are less common. Occasionally a persistent hiccough is seen. Tremors of various types frequently occur. They may be very fine or assume a choreiform or athetoid character. Convulsions are common in children. Paralysis or pareses are very frequent. Involvement of the oculomotor apparatus has already been referred

to. Weakness or paralysis of the muscles of deglutition is comparatively rare. Facial palsies may be either of the central or peripheral type. Practically any form or combination of forms of extremity paralysis or paresis may occur, and this is usually of the spastic type, although not invariably so. The disturbances of speech are a little difficult to group. Some in which there is an obvious dysarthria are probably due to disturbed function of the motor mechanism. In other instances there is a great delay in answering questions. Speech may be hesitant, slow or indistinct.

The reflexes, superficial as well as deep, may be normal, diminished or exaggerated and may be equal or unequal. An Argyll-Robertson pupil is often seen, while loss of accommodation reflex is less common.

The Babinski and confirmatory signs are often present, and the Brudzinski sign is common. The Kernig sign is frequently present. Both patellar and ankle clonus are occasionally obtained.

Other symptoms may be noted, most of these evidences of a systemic infection. Fever is a very constant sign. It is usually low and irregular. Occasionally it is subnormal for a part of the illness. Vomiting is fairly common early in the disease. An obstinate constipation is quite characteristic. Jaundice is sometimes seen but is rare. Bladder disturbances are not infrequent. There may be either incontinence or retention. Hematuria has occurred in two or three instances. Disturbances of the respiratory rhythm occasionally occur. They may take the form of very rapid respiration of forced inspiration. The Biot type is fairly common. Cheyne-Stokes is rare except in the terminal phases. Profuse sweating is a rather characteristic sign and occurs not infrequently. Epistaxis has been noticed as an early sign but has been seen in a very few cases.

It may be well to say a few words about the symptomatology in children, as it is our impression that the diagnosis is often missed. In many cases the symptoms are milder than in adults; in others they are more atypical. Probably the most common form in children is that resembling an early tuberculous meningitis. In these cases the diagnosis can be made only by repeated examination of the spinal fluids. In a certain number of cases the children show symptoms quite unlike those we consider characteristic of epidemic encephalitis. The following is a case in point:

G. L., a girl, aged five and a half years, was seen, February 14, 1921. She had had poliomyelitis in 1916, with paralysis of the right arm and leg. The paralysis of the leg had nearly cleared up. The present illness had begun three weeks before with headache, vomiting, convulsion, delirium and irregular fever reaching 103°. No lumbar puncture had been done. On February 14 she was crying out constantly in a meaningless fashion and was

apparently blind. A lumbar puncture was done, yielding 20 cc. of clear fluid with characteristic findings. The temperature began to subside after the puncture but the screaming persisted for several days and then she began weeping. This lasted for two or three days. Then the condition began to improve. The sight returned, the child began to speak rationally, but was slow in remembering and speaking. The improvement continued until March 13, when after an automobile ride she had a convulsion and became unconscious. Cheyne-Stokes respiration developed, the pulse was feeble and there was cyanosis. Another lumbar puncture was done that afternoon, yielding a clear fluid under increased pressure. This was followed by immediate improvement, and the next day she seemed as well as she had been before the convulsion. The improvement continued, although for several weeks she had a slight rise in temperature every second or third day. Three years later she was reported to be in excellent condition with no after effects.

Differential Diagnosis. The symptomatology of epidemic encephalitis is so varied that a complete differential diagnosis would necessitate a discussion of a very large number of diseases of the central nervous system and many of the acute infections. We shall attempt to discuss the differentiation from only the most important of these.

Tuberculous meningitis is probably the disease from which epidemic encephalitis is most often to be differentiated. The diagnosis may be absolutely made by examination of the spinal fluid and therefore time will not be taken to discuss the different points of clinical diagnosis as they are often misleading. Diplopia, for example, occasionally occurs in tuberculous meningitis. The finding of tubercles in the choroid also makes the diagnosis of tuberculous meningitis certain. The differentiation from the other forms of meningitis is less difficult, but even here mistakes are sometimes made. In purulent meningitis diplopia or disturbances of vision sometimes occurs. A lumbar puncture, of course, immediately makes the diagnosis.

The differentiation from poliomyelitis is usually made, especially from the spinal form. From certain forms that have been described in the past as the encephalitic type of poliomyelitis, the diagnosis at present is a matter of personal opinion. Certain authorities consider that cases previously diagnosed as the encephalitic type of poliomyelitis were really cases of epidemic encephalitis, and it is possible that the classification of poliomyelitis will have to be revised.

The differential diagnosis from brain tumor or abscess of the brain is often made only after extensive radiographic studies or at autopsy. These conditions are so infrequent that the percentage of error in a large series of cases is exceedingly small.

Syphilis of the central nervous system in some cases can only be differentiated by laboratory aid, the Wassermann test.

Cerebral hemorrhage and thrombosis are often mistaken for epidemic encephalitis and *vice versa*. The differential diagnosis is often extremely difficult, especially from cerebral thrombosis. A hemorrhagic fluid makes the diagnosis of cerebral hemorrhage very probable, although blood-tinged fluids may be found in cases of encephalitis.

Cardionephritic conditions, especially in the pre-uremic stages, frequently resemble epidemic encephalitis. Studies of the blood chemistry and determination of renal function will prove the determining factors in establishing final diagnosis in this type of case.

Certain forms of mental disease, dementia precox, for instance often present signs and symptoms similar to those of epidemic encephalitis. The case may have to be followed for some time before a definite diagnosis can be made.

Mention must also be made of encephalitis following acute infections, especially measles. The history of a recent acute infection will be the determining factor in making the diagnosis as the symptomatology and spinal fluid findings may be similar in the two conditions.

Laboratory Aids in Diagnosis. The blood examination is not at all characteristic in epidemic encephalitis. The blood count usually shows a low leukocytosis from 10,000 to 15,000 but sometimes a little higher. The blood cultures are sterile. The analysis of the spinal fluid is the most diagnostic laboratory aid. The spinal fluid is usually clear and increased in amount; sometimes it is slightly hazy and it may at times be yellowish. There have been instances where we obtained a blood-tinged fluid. The cells are usually slightly or moderately increased, the cell count being ordinarily less than a 100, with a preponderance of mononuclears. Occasionally there may be a larger increase in the number of cells up to 1000 or more. A preponderance of polymorphonuclears may at times occur. With but few exceptions we have found a slight or moderate increase in albumin and globulin content. Fehling's solution is promptly and well reduced, denoting a normal or even more than a normal amount of sugar in the spinal fluid. Of late we have used the quantitative method of determining the amount of sugar in the spinal fluid, and we have found the figures to range between 50 mg. and 100 mg. of sugar per 100 cc. Bacteriologically the fluid is sterile. These findings, while characteristic, are by no means pathognomonic, since similar findings are obtained in poliomyelitis, in some instances of syphilis of the central nervous system and early in tuberculous meningitis.

It may not be amiss to discuss in more detail the importance of the sugar content of the spinal fluid. Certain writers have stated

that an increase in the sugar content is pathognomonic of epidemic encephalitis. While it is frequently found in epidemic encephalitis, it is also found occasionally in poliomyelitis, syphilis of the central nervous system and even in meningism. The determination of the spinal fluid sugar is of most value in differentiating tuberculous meningitis. In this disease, when well advanced, the spinal fluid sugar is usually, but not invariably, greatly diminished.

Mention should also be made of the Wassermann test which should always be done when there is any suspicion of syphilis. The colloidal-gold reaction is not so important, since luetic and parietic curves are fairly common findings in epidemic encephalitis.

In differentiating tuberculous meningitis from epidemic encephalitis, if the routine spinal-fluid examination is not definite, recourse must be had to guinea-pig inoculation.

In a few instances where the diagnosis was unquestionably epidemic encephalitis we have found a normal spinal fluid. Other writers have reported a fairly large proportion of normal spinal fluids. However, a study of the spinal fluid analysis in many of our leading hospitals has convinced us that such examinations are often incomplete.

Pathology. Epidemic encephalitis belongs to the class of inflammatory diseases in which also are included poliomyelitis, syphilitic lesions of the central nervous system and trypanosomiasis. While these different diseases have, broadly speaking, certain characteristics, the cases in a given class differ so widely that it is difficult, if not impossible, to accurately diagnose by a study of the pathology alone, the less typical cases.

The meninges are usually described as showing only slight changes—an increase in the cellular content, particularly in the neighborhood of the bloodvessels of the pia-arachnoid. The cerebral cortex is generally normal, except for congestion of the vessel of the leptomeninges. In the brain substance the changes are most marked in the basal nuclei of the brain, the upper part of the pons and peduncles, the gray matter of the floor of the fourth ventricle and the aqueduct of Sylvius. The changes in the medulla and cord are often reported as less pronounced, though observers have noted the same changes occurring in the upper section of the cord. This was certainly observed in one of our cases, an adult, which came to necropsy. (Reported in the *International Clinics*, vol. 2, series 29.)

The lesions are generally described as consisting of four kinds:

1. Infiltration of the walls of the small vessels with lymphocytes and plasma cells.
2. Foci of interstitial and parenchymatous infiltration with round cells. In this reaction neuroglia cells may take part.
3. Lesions of the nerve cells—usually not so extensive as in poliomyelitis and with less neuronophagia. These lesions of the

cells usually occur when the inflammatory process takes place in the gray matter, but they may develop in the absence of an inflammatory reaction. Such is the case with regard to the cells of Purkinje in the cerebellum where inflammatory changes are almost entirely absent.

4. Foci of perivascular hemorrhage. The vessel walls are usually not necrosed.

In connection with the statement that lesions of the cells may occur in regions where there is no evidence of inflammatory reaction, it is interesting to recall that Abramson,³ in a very excellent study of the pathology of poliomyelitis made at the Research Laboratory during the epidemic of 1916, brought out the same fact in regard to the lesions of poliomyelitis.

Treatment. While many methods of treating epidemic encephalitis have been tried, there has been such a lack of uniformity in results that it is safe to say that at present there is no specific treatment. The majority of observers have agreed that lumbar puncture is beneficial. Some cases seem to do better with repeated lumbar punctures; others are apparently unaffected. None of the cases we have observed have suffered ill effects from lumbar puncture. No definite rule as to the repetition of lumbar puncture can be followed. We have been guided by the clinical condition and the reaction to lumbar puncture, also by pressure symptoms and amount of fluid removed. In some cases the beneficial effects following lumbar puncture have been striking. The following case illustrates this:

N. P., a man, aged twenty-nine years, was seen, January 1, 1923. Past history and family history are unimportant. Present illness developed rather suddenly on December 25, with chills, headache and fever, 103.5°, but without vomiting. On January 1 the patient still had a temperature of 103°, stiffness of the neck, slight ptosis of the lids and double vision. Patellar reflexes were slightly exaggerated. There were signs of bronchitis in both lungs. The patient was quite nervous and very excitable. The headaches and excitability were gradually getting worse while the diplopia was diminishing. Physical examination was otherwise negative. Lumbar puncture was done and 40 cc. of clear spinal fluid under markedly increased pressure was obtained. On examination the spinal fluid showed a large increase in cells; albumin and globulin, ++; sugar was normal. The patient apparently derived so much relief from the puncture that one was done every other day, seven in all. On January 14, twenty days after the onset, the patient was apparently all right except for slight weakness. He made an uneventful recovery without any sequelæ, and is at work and entirely well today. This is apparently an instance where repeated lumbar punctures proved beneficial.

Except for lumbar puncture, the treatment is symptomatic. The symptoms are so varied that the length of this paper will not warrant a full discussion.

The mortality in our series of cases is given in the following Table IV.

TABLE IV.—MORTALITY.

Age.	1918.	1919.	1920.	1921.	1922.	1923.	Total.	Mortality as to age, per cent.
Under 6 months	1	1	2	20.0
6 to 12 "	1	..	1	1	1	..	4	33.3
1 to 2 years	..	3	7	4	2	1	17	45.8
2 to 5 "	..	3	3	2	3	4	15	31.2
5 to 10 "	..	3	9	2	5	..	19	27.5
10 to 15 "	..	1	3	1	5	13.4
15 to 20 "	1	2	3	1	7	18.4
20 to 30 "	..	2	8	4	5	2	21	26.2
30 to 40 "	..	1	3	3	..	1	8	15.3
40 to 50 "	..	3	3	1	2	1	10	27.0
50 to 60 "	..	1	..	4	6	4	15	68.2
Over 60 "	1	3	4	57.1
Total deaths .	2	19	42	22	24	18	127	
Total No. of cases	11	68	111	108	70	83	451	
Mortality . .	Per cent 18.2	Per cent 27.9	Per cent 37.8	Per cent 23.8	Per cent 34.3	Per cent 21.9	Average mortality	28.2

Course of the Disease. When epidemic encephalitis first appeared it was considered a somewhat acute infection of the central nervous system, more or less like poliomyelitis. As time has gone on and cases have been studied further this opinion has been revised. Now we know that in many instances it assumes a very chronic course with periods of remissions and exacerbations. Sometimes relapses with acute symptoms occur after one or more years of apparently good health. It is not certain whether these are due to a lighting up of the old infection or to a new infection. One of our patients died of a second attack after being apparently well for a year. In other instances a year or more after the patient has apparently recovered, a slowly progressive condition, for example, a Parkinsonian syndrome, develops. This is usually considered a sequela, but the opinion has been expressed that this is a secondary attack or a relapse. In other cases these chronic conditions and progressions follow the more acute stages without any marked improvement in the patient's condition. In general, the course of the disease is similar to that of syphilis of the central nervous system. It must not be forgotten, however, that a fairly

large number of cases have remained well over a period of four or five years. The chronicity and variability of this disease is well brought out by the following case:

The patient, H. F., a female child, aged two years, was taken ill suddenly on August 18, 1923, with fever, 102° , and profuse sweating. The child was also gradually becoming progressively drowsy. The family and past history were negative. The physical examination on the fifth day of her illness showed the child to be acutely ill and apathetic. The temperature was 101° ; pulse, 90; respiration, 20. There was definite rigidity of the neck. There was double internal strabismus. All the deep reflexes were normal, but the abdominals could barely be elicited. The Kernig, Brudzinski and Babinski signs were all negative. There was a definite weakness of the muscles of the back. A diagnosis of meningitic type of poliomyelitis was made at that time. Lumbar puncture was performed and 30 cc. of clear fluid under increased pressure were obtained. On examination the fluid showed a moderate increase in cells, 98 per cent of which were mononuclears, a slight increase in albumin and globulin and a prompt and good reduction of Fehling's solution. On smear and culture no organisms were found.

October 2, 1923: There was a marked generalized rigidity, particularly of the neck. The strabismus had practically cleared up. The child also presented a typical picture of the Parkinsonian syndrome. There was also Parkinsonian tremor of the hands. It was now obvious that the child was suffering from encephalitis. Lumbar puncture performed at that time yielded 30 cc. of clear fluid under marked increased pressure.

October 17: Child still had Parkinsonian syndrome but to a lesser degree. The tremor was less marked and the child was able to walk a little. The neck was still rigid. Her general appearance was much brighter. On lumbar puncture 45 cc. of clear fluid were obtained.

June 12, 1924: The child was very much improved, but the Parkinsonian appearance was still quite obvious. There was neither rigidity of neck nor tremor of hands.

April 1, 1925: The child showed marked improvement. She was well nourished, bright and cheerful. The Parkinsonian features were disappearing, though her speech was still slow and the facies slightly masked. Her teeth were badly decayed. There was now a new complicating feature—a definite right hemiparesis of the lower motor neuron type as all her deep reflexes on that side were absent. She was unable to walk except when supported and guided. She also had slight inconstant tremor of her right hand.

This case illustrates a number of very interesting points. In

the first place it shows how difficult it is sometimes to make a diagnosis of encephalitis in children. This would have been considered a case of poliomyelitis were it not for the Parkinsonian syndrome that developed two months after the onset of her illness. The chronicity of this disease is also very clearly brought out. The clinical picture has changed a great deal during the different periods of a two-year illness, indicating the involvement of different foci each time. The Parkinsonian syndrome, for instance, was a rather early complication, while later in the course of her illness a right hemiparesis developed as the Parkinsonian picture was clearing up.

We cannot, therefore, consider any of these cases as completely recovered or the sequelæ as permanent until many years have elapsed. It will, indeed, be very interesting and instructive to study the children who had encephalitis a number of years from now.

Sequelæ. It is difficult to obtain a very adequate idea of the sequelæ in epidemic encephalitis. Those who work in neurologic clinics are likely to be unduly impressed with the frequency of sequelæ, since patients with sequelæ go to clinics, while those with complete recovery do not. To obtain a true idea of the frequency of sequelæ it would be necessary to follow a large number of cases for a long time. In the first place, certain patients have symptoms lasting for a year or more, which eventually disappear. For instance, one patient was blind for a year but eventually recovered his sight. Two had change of disposition for about a year and one of them did poorly in school, but both eventually made complete recoveries. In several other instances there were sequelæ lasting several months which eventually disappeared. On the other hand, other patients are in apparently good health for some time, and then develop symptoms which may be considered sequelæ or recrudescences, apparently of a progressive character. Care should, of course, be taken to ascertain that the patient was free from abnormality before the illness. A rather large percentage of our cases had previously suffered from some defect or from some acute infection of the central nervous system before developing epidemic encephalitis. For instance, 2 were definitely mentally defective before the illness; 1 had Little's disease and had developed epilepsy; another had had epilepsy for several years; 1 had had chorea; 3 had had poliomyelitis; 1 had had epidemic meningitis; 1 died from epidemic meningitis while convalescing from epidemic encephalitis.

Of our 451 cases, 127 died. Of the 324 surviving, 36 for one reason or another could not be followed up, leaving 288 cases which were fairly adequately investigated. It was found that 78, or 27 per cent, showed definite sequelæ, while the remainder were carrying on their usual occupations, or in case of children were pro-

gressing in school satisfactorily, and to all intents and purposes showed no evidence of abnormality. Many patients showed several residual defects. Although the number of cases was nearly equally divided between those more than, and those less than, fifteen years of age, it was noted that there were 50 with sequelæ in those more than fifteen years of age and only 28 in the other group. The fact that half of our cases were in children accounts to some extent for our percentage of cases showing sequelæ being less than the percentage of other workers.

The following table shows the distribution of the sequelæ:

TABLE V.

A. MENTAL	
I. Blunting of intelligence	30
II. Nervousness and irritability	13
III. Defective memory	5
IV. Changes in character or in disposition	14
V. Mania or psychosis	2
B. TROPHIC	
C. ENDOCRINE	6
D. SENSORY	
I. Headaches	11
II. Neuritic pains	6
E. MOTOR	
I. Eye changes	
(a) Pupillary	4
(b) Ptosis	2
(c) Strabismus	2
(d) Nystagmus	1
(e) Diplopia	4
(f) Limitation of motion	4
(g) Blurred vision	4
II. Paralyzes or pareses of muscles of face or extremities	13
III. Parkinsonian syndrome	11
IV. Tremors, twitches, spasms	11
V. Epilepsy	1
VI. Changes in gait	3
F. MISCELLANEOUS	
I. Asthenia	9
II. Digestive disturbances	4
III. Disturbances of sleep	10
IV. Speech disturbance	4
V. Respiratory disturbances	1
VI. Sphincteric disturbances	1
VII. Dizziness	3

A study of the classification shows that the greatest number of sequelæ were mental. The next largest group was of motor origin. It is not within the scope of this paper to classify exactly the various types of mental changes. In some instances they were so slight as to be hardly noticeable. In other instances there was a severe mental deterioration that was apparently progressive. How permanent some of the milder sequelæ will be, it is at present impos-

sible to estimate. We have already mentioned that in several instances sequelæ lasting for a year or more eventually disappeared.

While we have observed only 11 cases of well-developed Parkinsonian syndrome, certain other cases grouped as asthenia presented some of the features suggestive of an early or mild form of this condition. Perhaps the more common of the motor sequelæ is a paralysis or weakness of some group of muscles of the extremities or face. In one case there was a paralysis of the sternocleidomastoid muscle on one side, thus producing a torticollis.

A generalized muscular weakness is a rather common after effect. In some cases it is so severe that it would suggest myasthenia gravis, were it not for the history of the previous attack of encephalitis. In the great majority of cases, however, this general asthenia lasts only for several months or a year. This accounts for the small percentage of asthenia as a sequel in our tabulation.

We have also observed some very interesting but rare sequelæ. Four cases of obesity were noted; 1 case developed diabetes mellitus during her convalescence period. It is possible, of course, that this may have been a mere coincidence. We have not noted the report of this complication in the literature, in contrast to diabetes insipidus which has been observed by several writers. Some interesting trophic disturbances have also been observed, such as alopecia, furunculosis, stomatitis, decay of teeth and corneal ulcers. One patient, an adult, had a very interesting respiratory disturbance. He would get attacks of difficult and labored breathing, lasting from a few seconds to a few minutes. Various types of respiratory difficulties, especially in children, have been referred to in the literature. One patient, a girl, aged seven years, showed two years later some of the symptoms that are considered characteristic of multiple sclerosis—nystagmus, scanning speech and staggering gait. The knee jerks were exaggerated. There was, however, no intention tremor.

It is interesting to compare these frequent, diverse and serious sequelæ of epidemic encephalitis with those of poliomyelitis and epidemic meningitis. In the former the sequelæ are certainly sufficiently grave, but they are confined almost entirely to flaccid paralyses. In meningitis only a very small percentage of sequelæ occurs.

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THE ROLE OF FOCAL INFECTIONS IN THE ETIOLOGY OF ECZEMA.

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RECENTLY dermatologists have shown considerable concern over the comparatively large number of skin diseases of unknown etiology. Chipman¹ in his chairman's address before the section of Dermatology and Syphilology of the American Medical Association at St. Louis, pleaded for more determined effort on the part of dermatologists to discover the etiology of many diseases of the skin. Haase² in his chairman's address at San Francisco scored dermatologists for "the lethargy that now seems to possess" them and said that "the remedy for this condition is the thorough recognition that dermatology is nothing more, and certainly nothing less than a highly specialized branch of internal medicine." As an internist, therefore, I am offering no apologies for discussing briefly the etiology of a dermatological condition.

Much has been written of late on the cause of infantile eczema. Most authorities lay stress on sensitization to various foods as being the factor of greatest importance in infants and young children. Since most cases of infantile eczema slowly improve and eventually completely recover without dietary restrictions, it would seem likely, as pointed out by Barber³ that immunity to food substances is gradually acquired. Exceptions to this rule are found in the case of foods eaten only at rare intervals such as strawberries and lobsters to which some adults continue to be sensitive.

In contrast to the large number of contributions on infantile eczema, very few articles discussing the etiology of eczema in adults have appeared in recent literature. A large number of cases are probably due directly or indirectly to external irritants, and probably another large number are caused by local infectious agents. In the large class due to internal factors, I believe focal infection plays an important role. Sutton⁴ briefly calls attention to its importance as an etiological factor in eczema and Chipman¹ mentions focal infection as one of the factors to be considered in every skin lesion of unknown etiology.

The following cases are reported as illustrating the importance of infections of the teeth, tonsils, pharynx and pelvic organs in its etiology, and demonstrate the necessity for thorough examination and consultation in the treatment of this stubborn malady.

Case Reports. CASE I.—Miss A., bookkeeper, aged thirty-four years, came to me first on June 29, 1924, complaining of a severe itching eruption on the hands, arms, neck and face. The eruption

had appeared suddenly about six weeks before and had not responded well to treatment by another physician. Some of the lesions would subside for a time and then reappear suddenly, associated with considerable swelling, reminding one of angioneurotic edema. The itching was intense, sleep was disturbed, and the patient had become very nervous. She also complained of headache and pains which radiated up from the neck to the scalp. There had been some so-called dyspepsia, and excessive gas on the stomach and bowels. Careful inquiry revealed no change in diet, habits, environment or clothing which might have caused the eczema.

A complete physical examination showed tenderness over the right iliac fossa and the right hypochondrium. The pulse, temperature, blood pressure, hemoglobin, red cell, white cell and differential counts, urine and stool were normal. Roentgen ray of the teeth disclosed a well defined apical abscess involving the lower left first molar. The fingers were swollen and puffy, and there was some puffiness about the eyes. There were patches of skin on the arms, hands, forearm, neck and face which were covered with dry erythematous lesions. The lesions on the neck had the appearance of lichenification.

I advised immediate eradication of the focus of infection, but the patient wished to delay a few days. Local application of an antipruritic liniment and internal administration of calcium and alkalis gave no relief and on July 2 the offending molar was extracted under procain anesthesia. Exaggeration of the patient's neurotic and fatigue symptoms followed, lasting about ten days. The skin lesions improved at once with no further treatment and were entirely cleared up within a week after the extraction and have not returned. Her gastrointestinal complaints persist, and her general health, though improved, is not robust.

CASE II.—Mrs. M. M., aged fifty-two years, married, housewife, was first seen April 23, 1924, at which time she complained of the severe itching lesions described below. She was first troubled with eczema about five years before at the time of the menopause when it was confined to her ankles. It troubled her more or less until February, 1924, when the lesions became much more widespread. There was no history pointing to possible dietary or external irritant causes for the eczema.

Physical examination was negative except for numerous badly infected teeth and diseased tonsils. The skin eruption was extremely severe and widespread, involving both lower extremities from the knee down, the upper extremities from the elbow down, the upper anterior chest, neck, and face. The lesions were red, inflamed and weeping, and itched intensely. She was extremely nervous, emotionally depressed, and troubled with insomnia. A week of hospital treatment with a modified calamine lotion resulted in considerable

improvement in both general and local manifestations after which she had five teeth extracted under local anesthesia. A severe exacerbation of the eczema followed at once, which failed to respond to the same medication which had given so much relief, but gradually subsided, apparently irrespective of treatment. About two weeks later, she had several more teeth extracted, followed by another severe exacerbation, which in turn gradually subsided, since which time she has been free from symptoms except for an occasional mild eruption about the ankles. She still has a few teeth which are fairly normal. Her tonsils, which are diseased, have not been removed, and it is likely that they are responsible for the persistence of what little eczema remains.

CASE III.—Mrs. S., aged thirty years, housewife, came to me January 14, 1925, complaining of a severe itching eczematoid lesion on the anterior aspect of the neck and chin. The skin was dull red, with fine scales and excoriations. It had appeared suddenly two weeks before and there had been several acute exacerbations when there were small vesicles and considerable subcutaneous infiltration accompanied by a choking sensation and stinging pain in the neck. Her family and personal history were unimportant and the physical examination was negative except for several infected teeth. There had been no changes in diet, and she had taken no medicine which could cause the skin lesions. Possible external irritants were also ruled out. An antipruritic liniment for local application and a mixture of alkalin salts for internal use were prescribed. Improvement commenced immediately following the extraction of four teeth with apical abscesses and continued rapidly for a week, and then more slowly. Within three weeks after the extraction of the teeth she was entirely well and has remained so ever since.

CASE IV.—A physician, aged thirty-four years, who gave a history of repeated attacks of eczema prior to tonsillectomy, ten years previous, developed on February 15, 1925, a severe, acute pharyngitis accompanied by general malaise and fever. The second day scattered itching papular lesions developed on the legs, abdomen and buttocks. At the same time typical patches of dry, itching eczema measuring 5 x 7 cm. appeared on the anterior surface of the lower part of both forearms. There was nothing in the diet, medication or environment which could have caused the skin eruption. The febrile attack lasted two days, but a rather severe pharyngitis persisted about two weeks. The scattered skin lesions persisted only a few days, but the patches of eczema continued for about two weeks and gradually disappeared, without treatment, with the subsidence of the pharyngitis.

CASE V.—Mrs. G., housewife, aged thirty years, first consulted me July 25, 1924, complaining of a very severe generalized itching

eruption having all the classical characteristics of acute eczema. The lesions were almost universal, no part of the body being entirely free. They were flaming red in color and for the most part dry, though some areas presented a weeping surface. Itching was intense, interfering with sleep and producing marked nervousness. The birth of her fourth child had occurred two weeks previously. The labor was a normal one, and the puerperium was uneventful until the fifth day, when she complained of intense soreness in the lower abdomen. The following day she had a considerable elevation of temperature, and the skin lesions above described appeared. During the next week she said she had fever most of the time, but as the fever subsided her eruption also improved. When I first saw her, the pelvic infection had again become active, and her skin lesions were as bad as ever. Pelvic examination revealed an involuting uterus with bilateral acute salpingitis. Physical examination was otherwise negative. Prolonged complete rest in bed with symptomatic treatment resulted in complete subsidence of the pelvic infection. The skin lesions improved without local treatment, concurrently with the improvement of the pelvic condition, and the patient was discharged from treatment at the end of the fourth week of her puerperium. There has been no recurrence of either the pelvic infection or the eczema. Careful search was made for other possible causes of the skin eruption, but none were found.

Comment. A causal relationship between the focal infection and the eczema seems certain in the foregoing cases. The series might be increased by the addition of several cases where the causal relationship is somewhat less clearly defined. Speculation as to the mechanism of this relationship may be of interest. It is possible that the host has become sensitive to the bacterial end-products existing in the focus of infection. The almost explosive suddenness of the onset in 3 of these cases certainly suggests an allergic reaction. The fact that many men believe that infantile eczema is due to protein sensitization would add weight to this theory.

Summary. 1. Five cases of eczema apparently caused by focal infection are reported. In the first 3 cases, recovery followed the removal of abscessed teeth. In the fourth patient, the eczema ran its course concurrently with an acute pharyngitis. In the last case, rapid subsidence of the eruption accompanied improvement of infected pelvic viscera.

2. Careful search was made in each case for other possible causes of the skin lesions, but none were found.

3. Local antipruritic treatment in 4 cases had no effect upon the skin lesions, aside from decreasing the scratching, and improvement seemed to occur in spite of, rather than because of it.

4. The opinion is ventured that focal infection is an important cause of eczema in adults.

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A STUDY OF THE EFFECT PRODUCED ON THE ENZYME CONCENTRATION OF THE DUODENUM BY THE ORAL ADMINISTRATION OF CERTAIN COMMERCIAL PANCREATIC PREPARATIONS.*

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If one may judge by the number of pancreatic preparations placed on the market by reputable firms of pharmaceutical manufacturers there must exist a demand on the part of clinicians for pancreatic extracts which contain in active form the enzymes secreted by this organ, and which if administered in cases where a deficiency of the duodenal enzymes had been demonstrated, would presumably act as an aid to an impaired digestive function. Our knowledge of the action of many drugs on the gastrointestinal tract is still based largely on theory,¹ rather than on experimental findings, and the same criticism may justifiably be applied to our use of glandular preparations.

To test the activity of any pancreatic preparation *in vitro* is an exceedingly simple proposition, but such tests do not necessarily indicate the effectiveness of the same substance when administered by mouth, as in the latter case a number of conditions, not met with in the laboratory digestion experiment must be reckoned with.

In a study of the effectiveness of some commercial pancreas preparations we have therefore attempted to determine the utility of these extracts by a study of the enzymatic activity of the duodenal contents before and after the oral administration of some of these preparations.

Our method of procedure was as follows:

With the subject fasting about fifteen hours the duodenal tube

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was passed and allowed to reach the second portion of the duodenum, the position of the tube being in every case determined by the fluoroscope.

One or two portions of about 10 cc. of duodenal contents were removed and examined for enzymatic activity to serve as controls; the pancreatic preparation to be tested was then given by mouth in the amount stated in Table II, together with 50 cc. of tap water, and samples of duodenal contents were then removed at intervals for analyses.

The duodenal content obtained as above described was assayed for enzymatic activity by the methods of McClure, Wetmore and Reynolds.² The several slight modifications to the original methods described in a previous publication³ were also used in this work. Hydrogen-ion concentrations were determined colorimetrically by means of the Clark-Lubs series of indicators, and a set of buffers that had been checked by the electrometric method.

In Table I are presented the results obtained on four commercial pancreatic preparations when tested *in vitro* for digestive activity.

These tests were carried out as follows: 0.1 per cent solutions of these preparations dissolved in McClure's phosphate mixtures were prepared except in the case of the peptic liquid. This compound is supplied in fluid form, and we, therefore, evaporated 10 cc. to constant weight in an air bath at 110° C., and from the figures for total solids so obtained calculated the dilution of the original preparation required to make a solution containing 0.1 per cent solids. One cubic centimeter portion of the dilutions described above were added to 9 cc. of the substrate used in the McClure method, and the remainder of the test carried on by exactly the same technic as was used for the testing of the enzymatic activity of duodenal contents.

TABLE I.—RESULTS OF IN VITRO TESTS OF PANCREATIC PREPARATIONS.

Preparations.	Per 1 cc. of 0.1 per cent solution of preparation.		
	Amylase Mmg. glucose.	Lipase M10.1N NaOH	Protease Mmg. N2
Number one	5.6	0.7	5.7
Number two	0.73	0.7	4.6
Number three	0	1.2	4.67
Number four	2.38	0.8	0.316

As will be seen by an inspection of the results collected in Table I, all the preparations with which we worked gave evidence when tested *in vitro* of decided digestive power. The figures given in the table are calculated according to the method used by McClure

and his collaborators and should, we feel, not be considered in the light of absolute values but rather as of comparative importance only. Had some other procedure been adopted there is no doubt that the absolute figures given would have been different, although the comparative relations between the various preparations would probably have remained the same.

TABLE II.—RESULTS OBTAINED ON THE ORAL ADMINISTRATION OF PANCREATIC PREPARATIONS AND OF FRESH BEEF PANCREAS.

Pancreatic preparation.	Date.	pH.	Lipase M10.1N NaOH.	Pro- tease Mmg. N.	Amylase Mmg. glucose.	Subject.	Remarks.
Raw beef . . .	1/26/25	7.6	0.3	2.4	4.0	1. Normal subject	Fasting sample.
Pancreas	7.4	0	2.8	4.6	15 minutes after administration.
30 gm.	6.2	0.2	5.6	1.2	45 minutes after administration.
Preparation No. 2	1/20/24	7.0	3.0	5.5	2.1	2. Normal subject	Fasting sample.
		4.0	0.1	1.6	0.81	40 minutes after administration.
gr. vii	7.4	2.8	5.7	1.6	60 minutes after administration.
Preparation No. 2	1/23/24	7.4	0	1.7	0.7	3. Chronic biliary infection	Fasting sample.
		7.2	0	2.7	0.9		30 minutes after administration.
gr. vii	7.2	0	1.7	0.7		60 minutes after administration.
Preparation No. 1	2/16/24	7.2	0.10	1.8	0.55	5. Normal Subject	Fasting sample.
		7.0	1.0	1.8	2.60		30 minutes after administration.
		7.2	1.1	2.5	0.65	60 minutes after administration.
gr. vii	7.5	1.3	3.1	0.65	90 minutes after administration.
Preparation No. 1	3/23/24	7.4	0.3	1.4	1.5	6. Normal Subject	Fasting sample.
		3.4	0.3	0.24	0		30 minutes after administration.
gr. vii	3.4	0.1	0.21	0	60 minutes after administration.
Preparation No. 3	6/23/24	7.0	0	1.0	0	3. Chronic biliary infection	Fasting sample.
		7.2	1.4	3.4	0.7		30 minutes after administration.
gr. vii	7.4	1.8	5.6	0.8		60 minutes after administration.
		5.5	0	2.0	0	90 minutes after administration.
Preparation No. 3	1/28/24	7.4	1.5	2.6	0.93	4. Chronic biliary infection	Fasting sample.
		7.4	0.3	2.1	0.8		30 minutes after administration.
gr. vii	6.4	1.4	4.0	1.1		60 minutes after administration.
Preparation No. 4	3/23/24	7.6	1.2	1.2	2.1	7. Normal subject	Fasting sample.
		7.8	1.0	1.4	1.2		30 minutes after administration.
15 cc.	7.8	1.0	1.7	0.9	60 minutes after administration.
Preparation No. 4	3/30/24	7.2	0.2	1.5	1.0	8. Normal subject	Fasting sample.
15 cc.	7.3	0.2	2.0	0.93		45 minutes after administration.

Lipase—cc. of 1/10 N. fatty acids formed from oil by 1/50 cc. duodenal contents.
 Protease—mg. of non-protein nitrogenous bodies formed from casein by 1/50 cc. duodenal contents.
 Amylase—mg. of glucose formed from starch by 1/50 cc. duodenal contents.

In Table II we have collected the results obtained in experiment with fresh pancreas and with four commercial enzyme preparation made on eight subjects.

As a control on the commercial preparations we used for our first experiment fresh raw beef pancreas which had been finely minced after removal of the connective tissue. The subject of this experiment was a medical student who showed no repugnancy over the unusual dose. As will be seen there was a rise of almost 100 per cent in the proteolytic activity, no increase in a lipase and but little in amylase.*

The results on the commercial preparations showed in every case more striking effects produced on the proteolytic activity than on the starch and fat-splitting forms, although in certain experiments an undoubted increase in amylase was observed.

Summary. In a series of observations made on the digestive power of raw beef pancreas and of four commercial pancreatic preparations our results were as follows:

When tested *in vitro* all preparations showed digestive activity as regards proteolytic and lipolytic actions, but one seemed lacking in ability to split cooked starch under these experimental conditions.

In vivo the most striking effect noted was a marked increase in proteolytic activity, although in certain preparations a moderate increase in the ability of the duodenal secretion to split starch and emulsified fat was noted.

In interpreting the difference in the results obtained in the *in vitro* experiments as contrasted with those obtained on the administration of the preparations by mouth one must consider the possibility of stimulation of pancreatic secretion by these preparations as distinguished from the simple increase in the enzymatic concentration of the duodenal contents produced by the enzymes contained in the amount of gland substance taken.

The results presented above may, we believe, be interpreted as furnishing experimental proof of the fact that pancreatic preparations taken by mouth increases the digestive power of the duodenal contents.

* In this connection it seems desirable to call attention to our experiments on the effect of protein administration on the concentration of pancreatic enzymes in the duodenal contents.⁴ It was found that the ingestion of protein in the form of lightly boiled egg white, produced an enormous increase in the proteolytic activity of duodenal contents.

In considering the results produced by fresh pancreas and by the dried gland preparation, it would therefore seem justifiable to consider the possibility of stimulation by protein alone.

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SIMPLE LACTATING ADENOMA OF THE BREAST.

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PHILADELPHIA.

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SIMPLE lactating adenoma of the breast is a rare type of tumor; in the past ten years there have been but 2 cases from the surgical services of the University Hospital. The uncommon finding of this tumor in our Clinic, and the failure of some men when reporting large series of breast tumors to mention this type, have prompted an investigation and the reporting of this case.

Case Report. *History.* The patient, a primipara, was admitted to the University Hospital on the service of Dr. Eliason, to whom I am indebted for the privilege of reporting the case. The chief complaint on admission was the presence of a mass in the right breast. The patient, a negress, aged twenty-four years, first noticed a small lump in the breast nine years before. This she described as having been about the size of a small marble. The lump apparently remained stationary in size until the onset of pregnancy. This was one year before admission. At this time she noticed a gradual increase in the size of the mass, which progressed until at the time of delivery, it had attained the size of a chicken's egg. Associated with this enlargement there was some tenderness. After delivery, and with the onset of lactation, it grew rapidly. At time of admission to the hospital, three months after delivery, it was the size of a large orange. Since the time when the tumor was first noticed it has always become hard and slightly painful at the time of menstruation.

Physical Examination. The patient was a well-developed adult negress, aged twenty-four years. She did not appear acutely ill. There was nothing abnormal found on physical examination, except the mass in the right breast. The tumor was rounded, about the size of an orange, and was situated in the upper inner right quadrant. It was discrete, movable noninfiltrative and was not adherent to the skin or underlying tissues. There was no dimpling of the overlying skin or retraction of the nipple. The nodes in the axilla and supraspinous fossæ were not palpable. The Wassermann tests of the blood of the patient and her child were strongly positive.

Operation. A modified Thomas incision was made at the inner angle of the breast. The tumor, which was well encapsulated, was easily separated from the adjacent tissues and removed. The cavity was obliterated by continuous catgut suture. The wound

was then closed in layers, leaving a rubber tissue drain in the inner lower angle. The skin was closed with a continuous silk suture.

Examination of the Tumor. The tumor which was removed is shown in the illustration. It was tense, well encapsulated, reddish yellow in color, soft in consistency, lobulated and well circumscribed. On section the cut surface oozed thick cream-colored secretion. When this was scraped off the surface was red to pink in color, somewhat spongy, granular and opaque in appearance, and the lobules were well separated from one another by fibrous bands. There was no macroscopic evidence of cyst formation. The tissue appeared to be saturated with this creamy secretion, which in all probability represented a condensation product of the whole milk of which the water content had been largely reabsorbed.

Microscopic studies showed a fairly uniform structure. The tumor was covered with a well-defined fibrous capsule which gave origin to septa which divided the tumor into well-defined lobules. The acini which constituted the predominant structure showed slight variation in size. They were more or less irregularly circular in outline, and rested upon a very fine stroma of connective tissue. The latter was scant, so much so, in fact, that the basement membranes of the acini appeared to be in direct apposition. The epithelial cells ranged from a large low columnar type to a large cuboidal type and were for the greater part in single layers, resting upon the basement membrane. A slight proliferation of the cells into the acinar cavities was noted in some places. The nuclei of the cells were disproportionately small, when compared with the size of the cell, and stained deeply. The cytoplasm, which was quite abundant, was granular and showed vacuoles. The membrane of many of the cells was very indefinitely outlined, and appeared to be undergoing degeneration. The cavities of the distended acini contained a granular secretion, fat droplets and cellular débris.

Cases Reported in Literature. Simple adenomata of the breast are exceedingly rare tumors. One of the first cases was reported by Billroth in a married, nulliparous woman, aged twenty-four years. The location, size and general description of the tumor corresponds very closely to ours, but the tumor described by Billroth showed no evidence of lactation. Powers described a simple adenoma which had been removed from the breast of a woman four months pregnant. Grossly and microscopically this tumor was very similar to our own, except for the absence of lactation. Gross reports one removed from the breast of a girl, aged sixteen years, which was first noticed by the patient three months before. It was oval in shape, quite nodular and measured $1\frac{3}{4}$ by $1\frac{1}{4}$ by $\frac{1}{4}$ inches. There was no mention of lactation. Speese reports a tumor removed from the breast of a primipara, aged twenty-one years. The growth was present in the breast for several years,

but produced no symptoms. Following childbirth and coincident with the onset of lactation, the tumor, which had been the size of a walnut, began to enlarge rapidly. On examination it was found to be a simple lactating adenoma. Deaver and McFarland add one to the list. This tumor was removed by Dr. John B. Deaver from a patient in the Lankenau Hospital. The size, location and microscopic and macroscopic pictures were almost identical with the tumor reported herewith.



Lactating adenoma of the breast.

Classification. The term adenoma is often used inaccurately in describing benign growths of the breast. The majority of the benign breast tumors contain adnomatous tissue but in varying quantities. This fact is the basis for the classification of the adenomata. The greater number are grouped under the term fibroadenoma from the fact that fibrous tissue is the chief constituent of the tumor. Adenofibromata are less common than the former but by no means rare. In these the glandular tissue is a little in excess of the fibrosis tissue. The simple adenomata are, as already mentioned, very rare, being by far the rarest type of benign tumor found in the breast. The prevailing tissue is glandular in type with very little fibrous stroma.

Discussion. Uncomplicated benign tumors of the breast give rise to a few symptoms. There may or may not be very slight

pain at the time of menstruation. During pregnancy and lactation, however, they usually show great change. The glandular constituents of the tumor are apparently stimulated by the hormone which acts upon the normal gland tissue, with lactation hypertrophy as the result. Severe pains are experienced, especially during lactation, incident to the sudden enlargement of the tumor. This is probably due to the fact that there is no duct communication with the mammary gland proper. The result is that the secretion is stored up in the tissues and the tumor becomes very tense and painful.

The tumor is found to range in size from that of a walnut to that of an orange. It grows very slowly; if at all, except at the time of pregnancy or lactation, when it increases quite rapidly. The growth is always well encapsulated, discrete, movable, non-adherent to the skin and noninfiltrative. The adjacent lymph nodes do not enlarge in the absence of complicating infection. The age of patients having had these tumors removed is between fifteen and thirty years, the average being twenty years.

McFarland in referring to breast adenomata makes no distinction between the fibroadenomata and the simple adenomata. He feels that the fibroadenomata when placed under the influence of the hormones which activate the breast to hypertrophy during pregnancy are affected in the same way. It is his opinion that simple adenomata are the result of hormone activity upon the fibroadenomata. Bloodgood is of the same opinion. There is no doubt that there is an increase in the parenchymatous tissue in these tumors during pregnancy and lactation, but it is rather difficult to believe that all simple adenomata are physiologically active fibroadenomata. The fact that the cases reported by Billroth and Gross gave no history of pregnancy or of having borne children makes one wonder if the tumor in these patients at least was not a simple adenoma from the start. There is, however, always a possibility of inaccuracy in historical data and the few cases of simple adenomata reported as occurring independent of pregnancy and lactation are not sufficient evidence to refute the opinion of the men quoted above, namely, that simple adenomata are fibroadenomata altered in structure through physiologic activity.

The differential diagnosis between simple adenomata, fibroadenomata and adenofibromata is impossible except by microscopic study.

This, however, is of little practical moment since the treatment for all three types is excision. The possibility of these tumors undergoing malignant change has given rise to much discussion, especially in the case of the simple adenoma which would seem from its structure to be most likely to do so. Any tumor which consists of a disproportionate number of epithelial cells should always be considered as having great malignant potentialities.

Bloodgood makes no mention of these tumors becoming malignant, but he advises their removal lest this change occur.

Conclusions. 1. The average age of the patients having had these tumors is between the fifteenth and thirtieth years.

2. Adenomata give rise to very few symptoms except during menstruation, pregnancy and lactation, when they increase quite rapidly in size.

3. The simple adenomata are the least common of all the types found.

4. The treatment of these tumors is excision.

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THE PHARMACOLOGIC AND THERAPEUTIC PROPERTIES OF THE SULPHOCYANATES.*

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PERSONAL experience for a number of years has convinced me that sodium sulphocyanate is one of the most efficacious remedies available for the treatment of arterial hypertension. There exists, however, a remarkable paucity of readily available information concerning the drug, especially in the English language; the treatment of the subject in the current manuals on pharmacology is incomplete, inadequate and questionable. It is with the purpose of obtaining, collecting and presenting information relating to the pharmacologic and therapeutic properties of the sulphocyanates, and directing attention to a valuable remedial agent, that this study is presented.

There is a profusion of synonyms used to designate sulphocyanic acid and its compounds. The acid in English is interchangeably termed sulphocyanic and thiocyanic acid; in German it is usually called rhodanic acid (*Rhodansäure*), also *Rhodanwasserstoffsäure*, *Schwefelcyansäure*, *Schwefelcyanwasserstoffsäure*, *Sulfocyanwasserstoffsäure*, etc. Its salts are in English variously called sulpho-

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cyanates, sulphocyanids, thiocyanates and thiocyanids; in German, rhodanates, rhodanids, or very commonly rhodan compounds. All these synonyms must be borne in mind in consulting the index to the literature.

Sulphocyanic acid, HCNS , is an uncertain and unstable substance, easily decomposed by boiling and by exposure to air. Its compounds are very stable and definite. It forms a large number of salts, and has chemical relationships with various complex organic compounds, especially the purin group. Its alkaline salts, the sulphocyanates of sodium, potassium and ammonium have been most studied from a physiologic and pharmacologic standpoint, and are the compounds especially considered in this paper. These are white crystalline substances, saline in taste and very soluble in water and alcohol.

Sulphocyanate solutions are turned to a brilliant dark red color by the addition of a drop or two of ferric chlorid solution, decolorizing again on the further addition of an excess of mercuric chlorid; but these color changes do not take place if the reaction of the mixture is markedly alkaline. This forms a very sensitive test for the presence of sulphocyanate; the reaction is well marked in solutions of 1 to 10,000, and weakly shown in a dilution of 1 to 100,000. I have made quantitative determinations in saliva by comparing in a colorimeter 5 cc. of the clear colorless filtered saliva to which 1 drop of the official solution of ferric chlorid was added, with a 1 to 5000 solution of sodium sulphocyanate similarly treated. Normal saliva yields the sulphocyanate reaction; the urine of persons taking this drug on the addition of 1 or 2 drops of ferric chlorid solution turns a characteristic brown to dark red color, slightly different from the cherry color yielded with diacetic acid, and markedly different from the purple-black color formed with salicylic acid. The faint brownish color frequently obtained in the routine testing of urines for diacetic acid with ferric chlorid is perhaps due to the presence of a trace of sulphocyanate.

As has been long known, sulphocyanate (of sodium or potassium) occurs normally in the saliva; considerable study has been given to this point. It also occurs in other secretions and body fluids, as the tears and gastric juice. The mode of its formation has not been completely worked out; but it is generally supposed to result from the katabolism of sulphur-containing proteins, and to be formed mainly in the salivary glands, from which it is secreted into the saliva and then swallowed and absorbed into the system. The ordinary sulphocyanate content of the saliva approaches about 0.01 per cent, or 1 in 10,000. If the secretion of saliva amounts, as estimated, to a liter or more in twenty-four hours the amount of sulphocyanate swallowed from this source would approach 0.1 gm. daily. The sulphocyanate content of the saliva varies under different conditions; it is, for instance, diminished or disappears

entirely during the administration of iodine and increased by the use of tobacco.

I have found sodium sulphocyanate anticoagulant when added to blood to the extent of 2 per cent. One part of saliva added to 4 parts of blood similarly prevents coagulation. I have also found sodium sulphocyanate isotonic with blood in concentration of 1.5 to 2 per cent.

Weak solutions of the alkaline sulphocyanates possess no bactericidal properties. Some of the more complex organic compounds of sulphocyanic acid are apparently much more bactericidal.

Pharmacology. The earliest studies of the pharmacologic properties of the sulphocyanates were presented in 1857 by Claude Bernard, whose observations, however, were very incomplete. Subsequent important studies were presented by a number of investigators, notably by Setschenow in 1858, Ollivier and Bergeron in 1863, Dubreuil and Legros in 1867, Laborde in 1880, Paschkis in 1885, Martinotti in 1896, Edinger and Treupel in 1900-1901, Lodholz in 1905 and others.

PERSONAL OBSERVATIONS. I have made some personal studies of the effects of administration of sodium sulphocyanate to guinea pigs. It was given both by mouth and by intraperitoneal injection. By the oral avenue there was some uncertainty as to the exact amounts swallowed, so that the intraperitoneal dosage was more definite and accurate.

In sufficient doses sodium sulphocyanate was found to be highly toxic for the guinea pigs, death occurring in from a few hours to several days, the time varying with the amount and concentration of the drug employed.

Doses of 100 mg. per kilogram of body weight produced no evident symptoms. The minimum lethal dose observed was 200 mg. per kilogram of weight. Some animals, however, survived doses as high as 300 mg. per kilogram. Dilute solutions (2 per cent) were less toxic or more slowly toxic than concentrated solutions (10 per cent).

Immediately after swallowing a concentrated solution of sodium sulphocyanate the animals would frequently for a few minutes sneeze, or hiccough, or cough; while immediately following an intraperitoneal injection there might be some momentary shock. Aside from these the effects were the same after both methods of administration. After a few hours (the period varying with the size of the dose), during which the animal would appear normal or perhaps somewhat sluggish, protracted diarrhea usually appeared in the toxic cases, frequently with edema, congestion and hemorrhage at the anus. With this, progressive and extreme loss of weight occurred, to as much as one-third of the original weight; loss of weight of 25 per cent was observed in one instance with ultimate recovery. Later there appeared evidences of spinal irri-

tation. The animals became rigid, at first showing a notable spasticity of the rear extremities, which would be stiffly extended and abducted, so as to impede locomotion. When turned on its side the animal would find it difficult or impossible to resume the upright position. It would lie stiffly sprawled out on its belly or on its side. Later the rigidity would increase and involve the entire body, general convulsive twitchings and movements would occur and the animal would die in coma. With large doses death would occur in four or five hours; with smaller lethal doses the course of the case would usually be within two or three days, the maximum observed being six days. In 1 nonfatal case the only result was abortion; in 1 fatal case abortion failed to occur in a pregnant animal. Necropsies showed little abnormal.

Similar results were obtained with potassium and ammonium sulphocyanates.

The results of the available pharmacologic investigations of the sulphocyanates may be summarized as follows:

Ingested sulphocyanates are excreted as such by the kidneys, and are markedly demonstrable in the urine of persons taking the drug. Their excretion takes place very slowly; after discontinuing the ingestion of the drug the urine does not become free of sulphocyanate until after a number of days. This suggests the possibility of an accumulation of the drug in the system. Ingested sulphocyanate is also secreted into the saliva, like the iodids; the sulphocyanate content of the saliva increases while taking the drug, and after discontinuance of the latter the increase in the saliva persists for some time after it has disappeared from the urine. Sulphocyanates, therefore, pass through the organism unchanged; Pollak was able to obtain from the urine the same amounts as were ingested. They do not undergo transformation into the much more deadly hydrocyanic acid and cyanids. Both *in vitro* and *in vivo* the reverse change is readily effected, that is, from hydrocyanic to sulphocyanic acid. Sodium cyanid intravenously injected has been found to be rapidly converted into sodium sulphocyanate; and in case of poisoning with hydrocyanic acid or cyanids the intravenous injection of sodium sulphid and hyposulphite has been advised, with the object of converting them into the less toxic sodium sulphocyanate. The sulphocyanates form a well-marked group of compounds distinct from the prussic acid and cyanid group, and there need be no apprehension of the formation of the latter from the former in therapeutic use.

According to Edinger and Treupel, ingested sodium sulphocyanate increases the urinary output of sulphur and nitrogen and lessens urinary acidity.

Prolonged administration of sulphocyanates to animals in considerable (sublethal) amounts produces no perceptible harmful

effects. In human subjects, however, the continued use of sulphocyanate in therapeutic amounts is capable of producing disagreeable symptoms.

In large doses sulphocyanate is a powerful poison and exerts very potent and marked pharmacologic effects. The action varies somewhat in different animals, but in general is as follows:

To a certain extent, as stressed by Bernard and the earlier investigators, it is a direct muscle poison, abolishing muscular activity.

Intravenously injected into dogs in sufficiently large doses (100 mg. per kilogram of body weight) it causes immediate and permanent cessation of the heart action, usually with a convulsion at the moment of cardiac arrest (Lodholz). This may be due to direct action on the heart muscle, as well as to stimulation of inhibition. In doses not immediately fatal its immediate effect is to cause a marked and protracted increase of blood pressure (even to double the original height) and to increase the rate and amplitude of the respiratory movements (Paschkis). Cardiac arrhythmia may, or may not, be produced; the cardiac inhibitory mechanism is believed to be stimulated.

In from one to several hours after the introduction of sufficient doses of sulphocyanate, by mouth or otherwise, marked diarrhea sets in, supposedly caused by stimulation of peristalsis, similar to that produced by nicotin. With the diarrhea occurs much loss of weight.

Diuretic action has been noted only in rabbits.

The final stage of sulphocyanate poisoning consists of intense stimulation and irritation of the motor cells of the spinal cord, of quite the same order of intensity as that produced by strychnine or tetanus. The animal shows weakness, unsteadiness, tremors, inability to regain the upright position after being placed on its side or back, and perhaps a preliminary paralytic phase; the posterior extremities are particularly involved. These conditions deepen into general tonic and clonic convulsions, general quivering, rigidity, coma, death.

It has been a moot question whether the pharmacologic activities of the sulphocyanates are produced by the sulphocyanic radicle, the bases or by "salt action." The effects produced are so distinctive, however, so different in like amounts from the properties of other salts of the same bases that to me they seem clearly to be due to the sulphocyanic radicle. Some salt action is, however, evidenced by a somewhat greater toxicity of the more concentrated solutions. The sulphocyanate of potassium has been generally regarded as more toxic than that of sodium; but I do not know of any comparative studies demonstrating this.

The period covered by the course of a lethal case of sulphocyanate poisoning ranges from immediate death to several days, varying with the size of the dose and method of administration.

The minimum doses of sodium sulphocyanate found lethal by various observers vary with different animals, but are usually stated to range around 500 mg. per kilogram of body weight. In my own experiments the minimum doses which I found fatal to guinea pigs were somewhat lower, from 200 to 400 mg. per kilogram, some dying from 200, others surviving 300 mg. In the same ratio the minimum lethal dose of sodium sulphocyanate for a medium-sized man (weighing 70 kg., or 154 pounds) would be from 15 to 30 gm. ($\frac{1}{2}$ to 1 ounce).

Toxicology. I have found 4 cases in the literature bearing on the toxicity of sulphocyanates in man, as follows:

The first case (reported by Lesser, 1898) was that of a magician, aged fifty-eight years, tabetic, who in his tricks used potassium sulphocyanate to convert iron-containing water into "red wine." Being in destitute circumstances, he with suicidal intent consumed a quantity of the salt (amount not stated) dissolved in beer. He died in about ten hours. Necropsy showed corrosions and hemorrhages of the gastric mucosa, and traces of potassium sulphocyanate were demonstrated in many of the fluids and organs of the body.

The second case was that of a woman, who, after taking 0.3 gm. of ammonium sulphocyanate, developed convulsions, and died in twenty-eight hours. The case is briefly reported in a manual of toxicology by Kobert, 1906. The original report was not found; the details given are very meager, and the case is doubtful, since abundant clinical and experimental experience would indicate that the quantity stated, 0.3 gm., would be entirely insufficient to produce any material effects. Perhaps the statement of the amount was erroneous.

The third case (Adler, 1911) was that of an engineer, aged twenty-four years, who took 30 gm. of pure ammonium sulphocyanate dissolved in 200 cc. of water at midnight. A quarter of an hour later he vomited once, and then retired and slept until morning. About 7 A.M. he was awakened by an alarm clock, and on arising vomited once more and experienced a little vertigo. A physician then administered copper sulphate as an emetic, which was followed by further vomiting. After this there was moderate epigastric pain and a transient disagreeable sensation in the region of the bladder. There were no other symptoms, except that on the following day there may have been some chromatopsia, the skin of himself and other persons (but not white objects) seeming to have a yellowish tinge. The temperature on the first day was 37.1° C.; on the second day, 37.3° C.; third day, 37.4° C. (99.3° F.); after that not over 37° C. The systolic blood pressure was 95 to 100. The blood, urine, heart, pulse and so forth were normal. The urine showed a sulphocyanate reaction for twelve days.

The fourth case (Vintilesco and Popeşco, 1916) was that of a

magistrate, aged twenty-seven years, living in a hotel, who showed signs of mental aberration and poisoning and was sent to a hospital. On admission there he showed extreme cerebral agitation, with delirium and occasional convulsions. He became progressively worse, with anuria, cold sweats, total loss of consciousness, rigidity of the extensor muscles of the head and spinal column. Death occurred about forty hours after admission to the hospital. In the patient's room at the hotel was found a bottle of 100 cc. capacity labeled "Ammonium rhodanatum, 100 gm.," still containing a few crystals. These were found to be ammonium sulphocyanate; the blood and extracts from the organs of the cadaver gave strong reactions for the presence of sulphocyanate. The necropsy was otherwise negative.

Therapeutic Use. The first fruitful suggestions for the therapeutic use of sulphocyanates were presented by Pauli in 1903. In his studies of the bearings of the principles of physical chemistry in medicine he found that of a series of common anions the sulphocyanate ion exerts the maximum inhibitory effect on the precipitation of protein, next to it being iodine and bromine ions. From this he concluded that sulphocyanates should exert therapeutic powers comparable in potency with those of iodides and bromides. He reports the results of treatment of 35 clinical cases with 1 gm. of sodium sulphocyanate daily. He found the treatment to exert a very satisfactory sedative action on the pains, vertigo, restlessness, insomnia, irritability, fears, palpitation, increased reflexes, tremors and so forth of neurasthenic conditions, cardiac neuroses, climacteric neuroses (congestions), tabetic pains, syphilitic headaches and similar conditions. In another class of cases exhibiting arterial hypertension Pauli obtained marked reduction of blood pressure, with relief of vertigo and other subjective symptoms. He noted various analogies between the action of iodides and sulphocyanate, even to the occurrence of sulphocyanate acne and rhinitis. Among other things, he notes the use of iodides to promote the elimination of earthy salts, and suggests that the beneficial action of the iodides and sulphocyanates in arteriosclerosis may be due to their power to remove calcareous deposits in the arteries.

A number of other observers following Pauli reported favorable results from the use of sulphocyanate in the pains of tabes, migraine, neuroses, angina pectoris and similar disorders in doses ranging from $\frac{1}{2}$ to 3 gm. daily, the larger doses being found necessary to produce the results in some cases.

In this country Le Roy and Bently (1908-1909) claimed that the sulphocyanates exert a solvent and eliminative action on the earthy salts, which action might be counteracted by excess of ammonia. On this basis they advocated the therapeutic use of sulphocyanates for the removal and elimination of calcareous and similar deposits in various degenerative conditions. This theory of the action of

sulphocyanate is perhaps significant in connection with the use of the related substances, thiosinamin and fibrolysin, for removing fibrous overgrowths. They advocated small dosage, 1 grain four times a day. Le Roy claimed remarkably favorable results—"surprising success" and "all but miraculous good effects," to use his own words—from the use of sodium sulphocyanate in brain and nervous diseases, arteriosclerosis, cretinism, rickets, calcareous deposits about the teeth, cataract, chronic venereal conditions, senility and similar degenerative disorders. Concerning its action in arteriosclerosis, which he attributed to elimination of deposited lime salts, he said: "No remedy can or will reduce the blood pressure so kindly or quickly, when given after a proper manner, as the thiocyanates."

For upward of fourteen years, since having my attention directed to Pauli's work by Dr. Philip S. Roy, I have used sodium sulphocyanate in the treatment of arterial hypertension with the most satisfactory results. The response of blood pressure to this or other treatment depends on the pathology and etiology of the particular case. The arterial factors concerned in hypertension fall into two categories: (a) Organic changes in the arterial walls; (b) spasmodic contraction of the arterial muscle from nervous, toxic or other influences; either or both of these factors may be present and operative in given cases, resulting in decrease of the volume of the intra-arterial cavity and (other factors being equal) consequent increase of the blood pressure. The total range between the maximum and minimum systolic blood pressures clinically observed in any case of arterial hypertension or sclerosis may be regarded as a measure of the spasmodic element in that case, any residue being of organic origin. Little or no reduction of blood pressure can be expected in the cases where the increase is due to organic change; but the spasmodic hypertension should be quite amenable to treatment. It is without doubt advisable that even nonorganic hypertension should be brought down and kept as low as possible, in order to lessen imposition of a load on the heart that might in the long run tend to weaken the myocardium. It is in this class of cases that sodium sulphocyanate will be most effective; cases with obvious or marked renal or other changes are much less amenable to this or any other similar kind of treatment.

I have found sodium sulphocyanate superior in efficacy for the reduction of blood pressure in appropriate cases to any other medicament, and I believe it to be the best drug in use for that purpose. I use it as a routine, supplanting the iodid of potassium previously so used. Frequently a marked reduction of blood pressure, 20, 30, 40 mm. or more, occurs after a very few doses; in other cases the decline is more gradual. I usually continue administration of the drug for several weeks in order to maintain a lowered arterial tension; and in protracted cases institute a course of the treatment whenever the blood pressure rises unduly, or give it

intermittently, say a week or two in each month. A large proportion of the cases yield very satisfactorily to the treatment.

I have not made any special trial of sodium sulphocyanate as a sedative and eliminant in the various conditions for which it has been recommended by Pauli, Le Roy and others, and am not therefore qualified to express an opinion as to its efficacy along those lines. However, I have not incidentally found the sulphocyanate to exert any marked sedative effects. Further observation will be necessary to develop the full therapeutic possibilities of the drug. Pauli hit upon the therapeutic use of sulphocyanate because in the series of anions considered by him it had the maximum inhibitory effect on the precipitation of protein; if the same reasoning were applied to the basic radicles the ammonium (or possibly the magnesium) salt of sulphocyanic acid might be found even more efficacious than the sulphocyanate of sodium.

I have used sodium sulphocyanate in doses of 5 grains (1 teaspoonful of an 8 per cent solution in water) three times a day, well diluted, after meals, amounting to 1 gram daily. The addition of 1 or 2 drops of phenol would help to prevent the growth of fungi; the addition of peppermint, cinnamon or similar aromatic may lessen nausea. The dose may be reduced to $\frac{1}{2}$ or $\frac{1}{4}$ teaspoonful if the development of disagreeable symptoms necessitates, or as the blood pressure decreases. On account of uncertainty as to chemical or physiologic incompatibilities I have not combined the drug with other medicaments, except for the concomitant administration of nitroglycerin.

A considerable proportion of the patients experience disagreeable effects from the use of sodium sulphocyanate, sometimes so marked as to necessitate reduction of the dosage or discontinuance of the drug. The symptoms mostly complained of are nausea and gastrointestinal disorder; also nervous disturbances. These symptoms may not appear until the drug has been taken for some time, possibly suggestive of an accumulation of it in the system. With a view to obviating the disagreeable results, Nerking introduced for therapeutic use a protein compound of sulphocyanic acid, to which he gave the name "rhodalzid," which he claimed was therapeutically efficient and devoid of unpleasant effects. Pauli claimed to have observed acne and rhinitis produced by sulphocyanate; I have not met with any such effects. Le Roy claimed that patients might suffer toxic symptoms if they ate onions while taking sulphocyanate; I have tried this, but with negative results.

The fact that sulphocyanate occurs close to iodid and bromid in Pauli's series does not seem to me to necessarily indicate that its properties must therefore closely resemble those of the latter substances. Iodids and bromids occur next to each other in that series; yet their properties are quite different.

As illustrative of the therapeutic action of the drug, the following notes from a few cases selected at random are presented;

Case Reports. Case I.—Mrs. F. F., aged about seventy-five years, presented the evidences of senility, arterial atheroma and hypertension, painful arteriosclerotic ulcer of toe, intermittent claudication, mortui digiti, arthritic pains. The blood pressure on February 11, 1924, was 200 systolic and 95 diastolic; after taking sodium sulphocyanate the pressure on February 22 was 155 systolic and 85 diastolic; on March 22, 155 systolic and 75 diastolic.

CASE II.—Mrs. S. S., aged about sixty-five years, showed obesity, goiter, history of albuminuria and cylindruria and intermittent heart. On June 10, 1922, the blood pressure was 202 systolic and 120 diastolic; after taking sodium sulphocyanate, on July 5 the systolic blood pressure was 140. On April 22, 1924, she reported recent marked epistaxis and vertigo; the blood pressure was 240 systolic and 125 diastolic; she was put on sodium sulphocyanate and nitroglycerin. On May 24 the blood pressure was 180 systolic and 100 diastolic; some vertigo continued and there was mortuus digitus. On June 24 the blood pressure was 165 systolic and 90 diastolic; the symptoms were absent and the urine normal.

CASE III.—Mrs. N. C., aged about sixty-five years, on March 22, 1924, gave a history of hypertension, asthenia and arthritic pains; the urine was normal; the blood pressure was 195 systolic and 115 diastolic; sodium sulphocyanate was ordered. On March 27 she developed herpes zoster; the blood pressure was 174 systolic and 110 diastolic. On April 16 the systolic blood pressure was 150.

CASE IV.—Mrs. W. B., aged fifty years, during 1919–1920 had several attacks of cholelithiasis; at that time the blood pressure was 110 systolic and 80 diastolic. On May 24, 1920, the blood pressure was 175 systolic and 95 diastolic; after taking sodium sulphocyanate the blood pressure on May 28 was 140 systolic and 86 diastolic. Cholecystectomy was done on June 7, 1920. On August 6, 1920, the blood pressure was 170 systolic and 90 diastolic; after sodium sulphocyanate, 150 systolic and 90 diastolic on September 12. On March 19, 1925, she reported recent biliary colic; the blood pressure was 200 systolic and 100 diastolic; after sodium sulphocyanate, 130 systolic and 80 diastolic on March 25, and 150 systolic and 90 diastolic on April 29.

CASE V.—Miss S. C., aged about seventy years, on June 1, 1923, complained of vertigo; the blood pressure was 208 systolic and 102 diastolic. On June 13 the blood pressure was 140 systolic and 90 diastolic. After taking sodium sulphocyanate, on January 18, 1924, she complained of palpitation; the blood pressure was 226 systolic and 110 diastolic; after sodium sulphocyanate the pressure was 125 systolic and 75 diastolic on January 24, and the urine was normal.

CASE VI.—Mrs. W. B., born about 1860, was treated continuously for increased blood pressure from 1913 to April, 1925, when she died from lobar pneumonia. She also had obesity, slight goiter, systolic aortic murmur, recurring arthritis, asthenia; in 1922, after a visit to Panama, she had a nephritic outbreak, with unusual increase of blood pressure, cylindruria (no albuminuria), increase of blood urea, edema of the lower extremities, mental confusion and depression. During the twelve years when she was under constant observation the blood pressure ranged mostly from about 200 to 150. Whenever the arterial tension reached the higher figures sodium sulphocyanate was administered, generally with satisfactory results, although at times the action was somewhat uncertain; however, there was no tendency to increase of the blood pressure range, which at the end of the twelve years' observation was no higher than at the beginning. Disagreeable results attributed to the drug were occasionally manifested, such as loss of appetite, gastric upset, "nervousness," "sense of detachment," quivering and tremor, uncertainty of vision.

CASE VII.—Mr. W. B., a lawyer, aged fifty-six years, had a history of headaches, gastric disturbance, vertigo, tachycardia, intermittent cylindruria, moderate hypertension; he was "nervous" and apprehensive. The blood pressure was 190 systolic and 110 diastolic; after taking sodium sulphocyanate it was 160 systolic and 100 diastolic fifteen days later.

CASE VIII.—Mr. A. C., lawyer, aged sixty-seven years, had cardiac disease, manifested by systolic aortic murmur, arrhythmia, anginoid attacks; he also showed mental confusion and psychotic periods; the urine was normal. His blood pressure ranged mostly from about 200 to 140; there were occasional periods of hypertension, which seemed to be favorably influenced by sodium sulphocyanate. For instance, on July 23, 1924, the blood pressure was 198 systolic and 118 diastolic; on August 5, after taking sodium sulphocyanate and nitroglycerin, his pressure was 150 systolic and 90 diastolic. He had a severe anginoid attack on April 23, 1925, with a blood pressure of 250 systolic and 120 diastolic; he was given sodium sulphocyanate and nitrites, and the blood pressure on April 29 was 180 systolic and 95 diastolic.

CASE IX.—Mrs. A. J. C., aged sixty-eight years, had indigestion, a tendency to myocarditis, hypertension, a systolic aortic murmur and bronchitic asthma; the urine was normal. A large ovarian cyst was removed on August 6, 1924. The attacks of hypertension subsided after sodium sulphocyanate and potassium iodide were given. The blood pressure on January 19, 1922, was 195; after the use of potassium iodid and sodium bromid the pressure

was 165 on February 1. On March 17, 1923, her blood pressure was 198 systolic and 100 diastolic; on April 5, after sodium sulphocyanate was taken the pressure was 175 systolic and 95 diastolic. On April 14, 1925, the blood pressure was 205 systolic and 110 diastolic; on April 19 after sodium sulphocyanate was taken the pressure was 150 systolic and 100 diastolic.

CASE X.—Mrs. S. F. R., aged sixty years, gave a history of hypertension, up to 220; the urine was normal; she had a fibroid uterus and ovarian cyst. Sodium sulphocyanate was given when the blood pressure was elevated, followed by satisfactory reduction; for instance, the blood pressure on November 26, 1923, was 205 systolic and 120 diastolic; on December 1, 185 systolic and 115 diastolic; on December 18, 154 systolic and 90 diastolic.

CASE XI.—Mrs. J. R. H., aged seventy-eight years, showed evidences of senility, indigestion, hypertension, systolic aortic and mitral murmurs, cardiac arrhythmia, bradycardia, attacks of Stokes-Adams syndrome and mental confusion. The urine was negative. The blood pressure on January 4, 1921, was 240 systolic and 85 diastolic, and the pulse was 40; on January 11, after taking sodium sulphocyanate, the pressure was 190 systolic and 70 diastolic. On January 6, 1922, the pressure was 230 systolic and 90 diastolic; on January 10, after taking sodium sulphocyanate, the pressure was 195 systolic and 65 diastolic. On April 20, 1922, she had a Stokes-Adams attack with mental confusion and mania, with a blood pressure of 250 systolic and 90 diastolic; no result was obtained from sodium sulphocyanate, and the patient died on May 3.

CASE XII.—Mrs. F. S., aged thirty-five years, had hypertension (around 250) and nephritis following two pregnancies with eclampsia; the urine was of low specific gravity, with casts and much albumin. The blood pressure ranged from 200 to 270. In this and similar cases with interstitial nephritis no especial reduction of blood pressure followed the use of sodium sulphocyanate.

The therapeutic effect of sodium sulphocyanate in lowering blood pressure is scarcely explainable on the basis of its physiologic and pharmacologic action in large doses as thus far elucidated. In animal experimentation large doses have been found to exert a directly opposite action. Nor does this therapeutic effect seem explainable on the ground of promoting the elimination of calcareous deposits in the sclerosed arteries, since the removal of such deposits would probably take place much too slowly to account for the prompt reduction of blood pressure that frequently occurs. Besides, a more permanent reduction of blood pressure should be

expected from decalcification of the arteries than occurs clinically. Lacking any other explanation, the reference of the sulphocyanates to the indefinite and empirical class of alteratives is rather a confession of ignorance.

Summary. The alkaline sulphocyanates are stable, distinctive, and biologically active substances, entirely different in their pharmacologic properties from the deadly prussic acid and cyanid group. In sufficient amounts they exert potent and distinctive pharmacologic properties, acting especially as intense spinal irritants, with lethal termination. Upward of 15 gm. might cause death in man. For therapeutic use sodium sulphocyanate in doses of up to 1 gram daily (5 grains three times a day) has been found markedly effective in reducing arterial hypertension.

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ABDOMINAL PAIN DUE TO EPIGASTRIC HERNIA.

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EPIGASTRIC hernia is quite frequently the cause of vague abdominal pain which is referred to the right upper quadrant and the condition is occasionally diagnosed as cholecystitis, gastric or duodenal ulcer, or appendicitis. If the diagnosis is not made, an exploratory laparotomy is sometimes performed. It is not uncommon for patients who have had a thorough physical examination, gastrointestinal roentgen rays, Wassermann and urine analysis, all of which are negative with persistence of the original symptoms, to present themselves to hospital clinics when upon careful inspection and palpation of the linea alba, there is revealed a small lump in the midline which is the cause of the abdominal discomfort.

Historical. The first operation for epigastric hernia apparently was performed by Ferrier in 1885 and he insisted upon the hernia being the etiological factor in causing vague upper abdominal pains. The ratio of epigastric hernia to other forms of hernia is put as low as 0.5 per cent and as high as 5 per cent. Imfeld, from Kocher's clinic, reported 450 consecutive hernia cases with 21 epigastric hernias, or 4.6 per cent. In this clinic in the past four years we have had 300 hernias including 4 epigastric hernias or a percentage of 1.33.

Anatomical. If one recalls the anatomy of the upper abdomen, the etiology of epigastric hernia is readily understood. Fig. 1 shows the recti muscles are wider above the umbilicus than they are below. Also the width of the linea alba is greater in the upper part of the abdomen. Fig. 2 shows the linea alba is formed by the interlacing of the anterior and posterior sheaths of the recti muscles. Fig. 3 shows the superior and deep epigastric arteries which are branches of the internal mammary and the external iliac, running in the sheath of the rectus muscles, and not perforating the transversalis fascia. Fig. 4 shows the vessels of the falciform ligament in a large scale, perforating the transversalis fascia and linea alba. The falciform ligament is attached to the anterior abdominal wall just to the right of the midline. In operating on epigastric hernia, one usually finds a tab of fat accompanied by a small bloodvessel which has come from the falciform ligament of the liver. The perforation of the transversalis fascia and linea alba causes a potential point of weakness and through this escapes the peritoneal fat which gradually enlarges and in so doing causes tension on the peritoneum and later a definite peritoneal sac.

Causation. The hernia is usually found in the midline between the ensiform and the umbilicus, approximately $2\frac{1}{2}$ to 3 inches above the umbilicus. There is generally found a small lump which can be reduced by applying pressure over same. This lump is usually

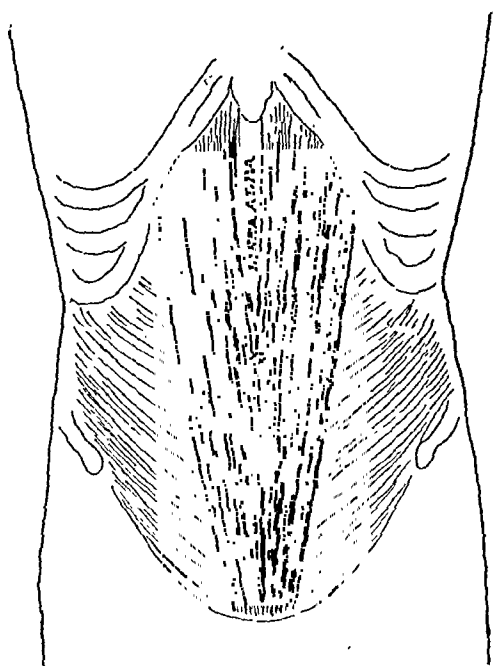


FIG. 1. —Showing space between the recti muscles.

tender to pressure and may not be detected if the patient is prone but is almost always detected if the patient is standing erect, which should be borne in mind when a patient is suspected of having epigastric hernia. Epigastric hernias have been divided into two forms, Quain,¹ (1) Peritoneal lipoma or properitoneal tumor, without

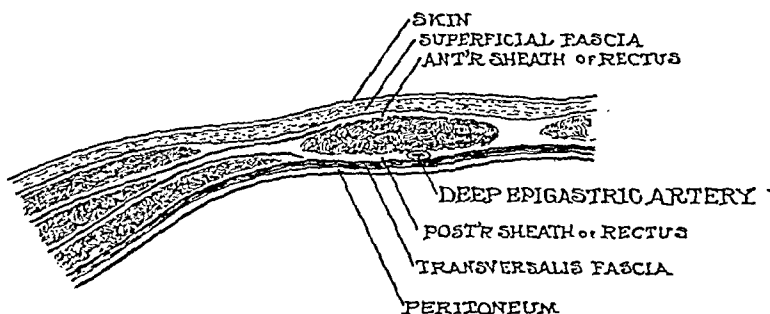


FIG. 2. —Showing formation of the linea alba.

a definite sac; (2) true hernia with the sac of peritoneum with or without contents. Moschcowitz,² who does not believe that there is ever a distinct sac present, reports³ a case of strangulated hernia which contained omentum which required resection. It would seem

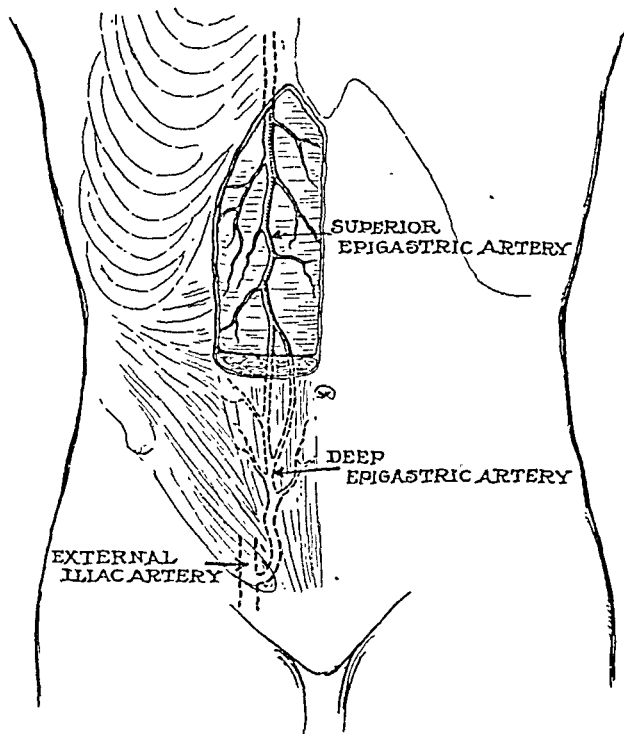


FIG. 3. —Showing epigastric arteries in the sheath of the rectus muscles.

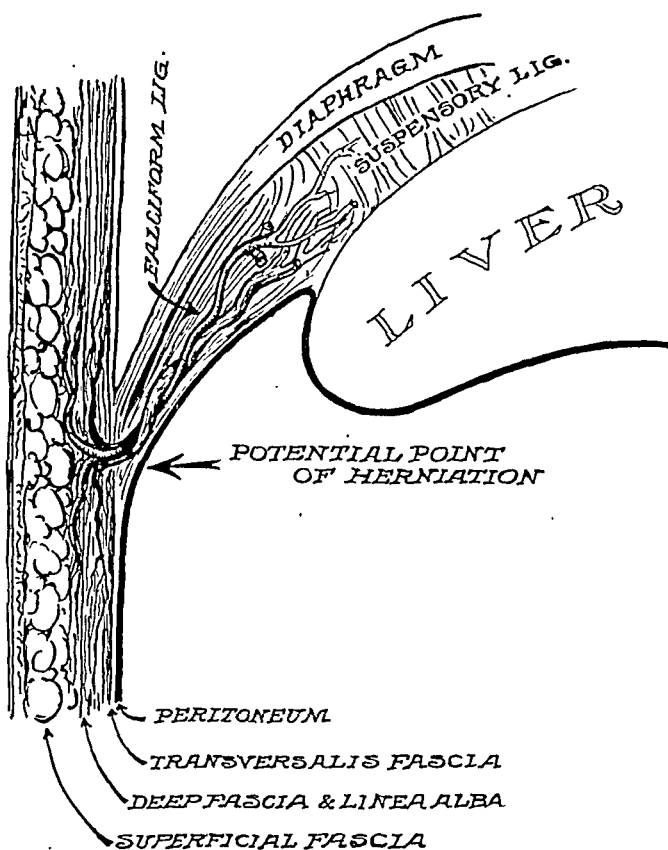


FIG. 4. —Showing the course of the vessels of the falciform ligament.

that the type of hernia encountered will depend on the duration of the history, and the peritoneal lipomata of Quain are only the first stages in producing a definite peritoneal sac, as several strangulated hernias have been reported which contained omentum and intestine. The potential point of weakness in the transversalis fascia and linea alba which have been perforated by the vessels of the falciform ligament allows the peritoneal fat to escape, which gradually enlarges from the intra-abdominal pressure and in so doing produces a definite peritoneal sac.

Signs and Symptoms. Signs and symptoms are rather vague and the case may present symptoms of any upper abdominal condition. It was formerly thought that the gastric distress was due to the fact that the stomach was caught in the herniation, but this does not seem to be true and the pain is usually referred to the biliary tract or the stomach because it is transmitted through the falciform ligament by the tension on the peritoneum. The patients present themselves complaining of pain and discomfort which is usually worse after meals. The distended stomach seems to be the cause of the discomfort. The kind of food does not bear any relation to the discomfort and the patient does not have a periodicity that is encountered in gastric or duodenal ulcer. The pain is worse while standing or bending and is quite frequently relieved if the patient is placed in a prone position. The erect position causes a pinching of the hernial contents by tension of the linea alba which immediately causes a referred pain to the right upper quadrant, through the peritoneal tension. These cases should have a thorough physical examination with gastrointestinal roentgen ray series, Wassermann and urine analysis before the pain is definitely attributed to the hernia. If the hernia is reduced the patient is usually free from pain and discomfort, but as soon as it reappears the discomfort returns. Lewisohn⁴ advocates exploratory laparotomies in all cases of epigastric hernia, due to the fact that lesions of the stomach, duodenum or biliary tract are frequently overlooked. This should not hold true if the case has been carefully examined before operation. A herniation the size of a pea is usually the one that is the cause of the symptoms and this is the one that is more often overlooked. The larger hernias are usually easily diagnosed and rarely cause abdominal discomfort.

Treatment. Surgery seems indicated as soon as the diagnosis of epigastric hernia has been made and the abdominal discomfort attributed to it. The operation can be performed under local anesthesia and the transverse incision, similar to the one employed in the Mayo operation for the umbilical hernia may be used. A mass of properitoneal fat which is accompanied by a small blood-vessel is usually found. Whether a definite peritoneal sac is found or not will depend on the duration of the hernia. If there is a definite sac, it may or may not have intra-abdominal contents in

same. If it does, omentum is usually found, but occasionally small intestine or even large intestine is encountered. If a sac does not exist a simple removal of the peritoneal lipoma is all that is necessary, but if a definite sac is present it may be treated the same as an umbilical sac. The linea alba is closed with interrupted chromic sutures. The follow-up of these cases is most satisfactory, providing the patient has been carefully examined before the operation is advised.

Conclusions. 1. The linea alba should be carefully examined in all cases of upper abdominal pain.

2. No case of epigastric hernia should be operated on until all possible sources of abdominal pain are eliminated.

3. Abdominal exploration does not seem indicated in cases of epigastric hernia.

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REVIEWS.

PROTEINS AND THE THEORY OF COLLOIDAL BEHAVIOR. By JACQUES LOEB, late Member of the Rockefeller Institute for Medical Research. Second edition. Pp. 380. New York: McGraw-Hill Book Company, 1924.

THIS posthumous work, containing as it does the conclusions of the last experiments of the author and his associates, constitutes a crowning achievement of a career devoted to lifting the veil of obscurity from so-called vital phenomena. Although the researches of the closing years of his life were a departure from his earlier interest in mechanistic physiology, the author displayed in his work a mastery of logical planning, careful experimentation and critical interpretation that will cause it to stand out as classic. Loeb has sifted the chaotic material on the colloidal behavior of proteins through the screen of classical chemical laws, with the aid of measurements of hydrogen-ion concentration, hitherto neglected because of inadequate methods, and the Donnan theory of membrane equilibria. These efforts in crystallizing a colloidal subject will leave their imprint on the future advance, not only of physical chemistry, but of physiology as well.

B. O.

ANAPHYLAXIS AND SENSITIZATION. By R. CRANSTON LOW, M.D., F.R.C.P., Lecturer on Diseases of the Skin, Edinburgh University and Assistant Physician for Diseases of the Skin, The Royal Infirmary, Edinburgh. Pp. 384; 23 illustrations. New York: William Wood & Co., 1925. Price, \$6.50.

THIS volume is a presentation of the subject, with special reference to the skin and its diseases. A reproduction of the thesis presented for the M. B. degree at the University of Edinburgh, where it was awarded the gold medal. The work represents both a review of the literature in this field as well as the presentation of some original work by the author. After introductory chapters on the theories of anaphylaxis and the manifestations of anaphylaxis in man, the various forms of cutaneous sensitization are taken up, including urticaria, drug eruptions, the erythemata, sensitization in

tuberculosis and syphilis, dermatitis venenata, sensitiveness of the skin to light and sensitization and immunity to fungus infection. On the latter subject the author has done some creditable investigative work. The book should find favor with immunologists as well as dermatologists. The illustrations in color are very well done.

R. K.

LECTURES ON DYSPEPSIA. By ROBERT HUTCHISON, M.D., F.R.C.P., Physician to the London Hospital and to the Hospital for Sick Children. Pp. 176; no illustrations. London: Edward Arnold & Co., 1925.

THE thirteen lectures making up this book cover the important organic and functional disturbances of the gastrointestinal tract from the author's personal point of view, which is a very rational one, and are intended for the general practitioner rather than the specialist. Brevity has necessitated many dogmatic statements, but the clearness of the diction, the apt quotations and the striking similes employed are most convincing and give to the presentation a charm which is lacking in the usual textbook. Anyone taking it up will read it through and will want to refer to it again. The final chapter on the chronic abdomen is very fascinating.

T. M.

THE BLOOD: A GUIDE TO ITS EXAMINATION AND TO THE DIAGNOSIS AND TREATMENT OF ITS DISEASES. By G. LOVELL GULLAND, C.M.G., M.D., F.R.C.P.E., Professor of Medicine and Clinical Medicine in the University of Edinburgh, President of the Royal College of Physicians of Edinburgh, and ALEXANDER GOODALL, M.D., F.R.C.P.E., Assistant Physician to the Royal Infirmary. Third edition. Pp. 424; 45 illustrations. New York: E. B. Treat & Co., 1925. Price, \$7.50.

IN the eleven years that have elapsed since the appearance of the second edition of this work, the temporary stop imposed by the World War to the flood of hematologic literature has allowed a certain number of appraisals to be made. Much valuable new work, however, has also appeared, and the authors take a characteristically conservative point of view toward such of it as remains unconfirmed. The same viewpoint apparently, or possibly a lack of desire to revise thoroughly, has maintained a number of procedures, which in this country at least are no longer used, and has caused the omission of what many consider desirable improvements. In fact it occasionally seems possible to detect certain sections that have obviously been brought up to date to the comparative neglect

of their neighbors. There is also a noticeably small number of foreign references (more than half are British); whether from an overzealous nationalism or lack of acquaintance with foreign literature, the results are equally regrettable. On the other hand, the book is well balanced, systematic and no grave omissions of first importance are noted. One would like to see presentations of the dynamic balance of blood formation and destruction, Sabin's recent studies on blood cell formation, the movements of leukocytes and so on. Removal of the section on the mechanism of blood clotting from the description of hemophilia to its proper position would improve matters. Although perhaps one of the best books on the subject in English, it emphasizes the need in our language for some such book as Ferrata's *Emopatie* or Pappenheim's *Grundriss der haematologischen Diagnostik*. E. K.

ENZYME INTELLIGENCE AND WHENCE AND WHITHER. By NELS QUEVLI, Reg. Phar., LL.B. Pp. 578; 83 illustrations. Minneapolis: The Colwell Press, Inc., 1925. Price, \$3.65.

"ILLUSTRATING that enzymes and ferments are the ultimate, indestructible and invisible units of life and are conscious and intelligent. That these units produce and maintain all living things we see. That our body is a republic established by enzymes coming from the invisible world of life to which we return when we die." Further comment is unnecessary. E. K.

PROCEEDINGS OF THE THIRD INTERNATIONAL CONGRESS OF THE HISTORY OF MEDICINE AT LONDON, 1922. Pp. 320; illustrated. Antwerp: de Vliet, 1923.

THIS volume presents those papers read at the London Congress which have not appeared in other publications. The fifty-three items make up a considerably smaller presentation than the proceedings of the second Congress at Paris, but as it contains no record of the titles published elsewhere, a comparison of the scientific production of the two congresses is impossible. From all other points of view, however, the volume is inferior to its predecessor. It is to be hoped that the published proceedings of the fifth Congress, recently held in Geneva, will return to the previous high standard. A number of papers are grouped around the set topics of mediæval epidemics, and the history of anatomy; the majority are disconnected varia, among which many will doubtless be found to interest those historically inclined. E. K.

A COMPEND OF DISEASES OF THE SKIN. By JAY FRANK SCHAMBERG, Professor of Dermatology and Syphilology, Graduate School of Medicine, University of Pennsylvania. Seventh edition. Pp. 316; 110 illustrations. Philadelphia: P. Blakiston's Son & Co., 1925.

THIS well-known little book fulfills all the requirements of a publication of its scope. The recent advances in therapeutics, such as foreign proteins, actinotherapy and chemotherapy are set forth in clear and sufficient terms. The ever-changing therapy of syphilis is brought down to date. Such adverse criticisms as might be offered are minor ones; thus, it might be better if blastomycosis were transferred (page 302) from the category of new growths to that of the inflammatory diseases. The book deserves the continued patronage which a seventh edition indicates.

F. W.

1924 COLLECTED PAPERS OF THE MAYO CLINIC AND THE MAYO FOUNDATION. Vol. XVI. Edited by Mrs. M. H. Mellish. Pp. 1331; 254 illustrations. Philadelphia and London: W. B. Saunders Company, 1925. Price, \$13.00.

THE present volume follows the previous policy of this well-known clinic in forming a complete reference record of all papers for the year, whether given in full, abridged, abstracted or by title. More than two hundred titles by one hundred and sixty authors are sufficient indication of the quantity of research work work turned out there annually. In quality, as one would expect, there is considerable variation. First-class articles, usually by the senior members, are interspersed with some of lesser merit and with abstracts that are so short that they serve for little more than to carry out the aforementioned policy. All readers, however, should find something suitable for their palates, and to those liking their mental pabulum in large single doses such a volume will be preferable to a periodical journal, as it undoubtedly is to many of them in substance.

E. K.

A COMPEND OF OBSTETRICS. Especially Adapted to the Use of Medical Students and Physicians. Revised and edited by CLIFFORD B. LULL, M.D., Instructor in Obstetrics, Jefferson Medical College, Assistant Obstetrician to the Maternity Department, Jefferson Medical College Hospital, etc. Tenth edition. Pp. 272; 84 illustrations. Philadelphia: P. Blakiston's Son & Co., 1925.

THIS book is intended for use as an aid to rapid review by those preparing for examinations. It will be found to be complete, concise, well arranged and has been thoroughly revised.

P. W.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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Primary Vascular Nephritis, or Renal Periarteritis Nodosa.—Periarteritis nodosa is of such rarity, only seventy cases having been recorded in literature, that the recognition of the disease antemortem is exceptional. Clinically the disease may be recognized by the following clinical picture, according to KEEGAN (*Arch. Int. Med.*, 1925, 36, 189). There is an acute or gradual onset of obscure sepsis with emaciation, weakness, prostration, fast pulse, marked leukocytosis and frequently intermittent abdominal pain. The arteries most frequently involved are the coronary and the smaller vessels of the kidney. An affected artery shows well-marked nodules with frequent small aneurysms or thrombotic obstruction and infarction. In addition to the interest aroused by the very full case report of an unusual disease, particularly of moment in the author's study, is the fact that the right kidney was removed at operation some weeks prior to the death of the patient and a wonderful opportunity was presented to contrast the early and late pathologic picture of the condition, together with the effect the disorder had upon the kidney itself. The acute lesions of the first kidney were found to be changed in the second into early arteriosclerosis. The intima was greatly thickened by young white fibrous tissue, leading to anemia of the cortex, with atrophy, fibrosis and infarction. The cortex was narrowed and the tubules markedly atrophied with a varying degree of replacement interstitial fibrosis. When the patient was first seen there was but scanty evidence of renal insufficiency. Subsequently cardiac decompensation, decreased

urinary output, nitrogen retention and a terminal uremia developed, undoubtedly the result of the rapid arterial obliteration. The pathology in this case naturally suggests to the author the possibility of a certain number of cases of chronic vascular nephritis being caused by a mild nonfatal attack of renal periarteritis nodosa. The term, chronic vascular nephritis, ordinarily is applied to the arteriosclerotic kidney of the aged, a condition characterized by extension of the sclerosis of the aorta and large vessels into the renal artery, by an absence of the clinical symptoms of kidney disease and by a cardiovascular death. The combination form of Volhard and Fahr, while primarily vascular in origin, is characterized by extensive glomerular change and the development of the signs of renal insufficiency, often ending in uremia, while cardiac compensation is adequate. If the author's conception of the origin of the vascular changes in an acute arteritis holds true it would fully explain the difficulty of the experimental reproduction of the glomerular type of vascular nephritis, because the organism causing periarteritis nodosa is extremely difficult to isolate, and probably is highly adapted to the human environment.

Pathogenicity of *Trichomonas Intestinalis*.—There is considerable difference of opinion among parasitologists as to the pathogenicity of *Trichomonas intestinalis*. The majority consider these flagellates to be harmless, but to a well-informed minority they seem to be apparently entirely capable of producing definite symptoms and pathology. TSUCHIYA (*Arch. Int. Med.*, 1925, 36, 174) undertook a reinvestigation of the subject from the clinical and laboratory point of view. He found that in a series of 30 cases there were no urinary metabolic, blood, gastrointestinal, nervous, nutritional or circulatory symptoms which could be attributed to the trichomonas infestation. Diarrhea, presumed by many to be the result of trichomoniasis, was present in only two of his cases. Furthermore, he noted that the type of intestinal flora does not alter the number of trichomona.

Diseases of the Liver: I. A Survey of the Tests for Hepatic Function; II. A Comparative Study of Certain Tests for Hepatic Function in Experimental Obstructive Jaundice.—These two papers, the first by GREENE, SNELL and WALTERS (*Arch. Int. Med.*, 1925, 36, 248), the second by the first two authors in collaboration with ROWNTREE (*loc. cit.*, p. 273), present obvious difficulties in abstracting, but will well repay those interested in liver functional tests who read them in the original. The authors give a most excellent summary of previous work done by others and show in experimental obstructive jaundice, among other findings that the van den Bergh test affords a simple and accurate means of studying the degree of bile retention and the progress of icterus, and that the phenoltetrachlorophthalein test shows dye retention in the blood stream that closely parallels the degree of bile retention.

Ketogenic Diet for Epilepsy.—Going on the assumption that the ketone bodies developed in the body during the imperfect burning of fats might possess the same sedative action on the central nervous system as do the anesthetics, PETERMAN (*Jour. Am. Med. Assn.*, 1925,

84, 1979) made use of a high fat diet for epilepsy with apparently remarkable results. Limiting the protein to 1 gm. per kilo body weight and the carbohydrate to 10 to 15 gm. daily, he made up the remainder of a high caloric diet with fat. Such a diet he usually found to produce acetone bodies in the urine in a few days. In cases where it failed to do so he found that the administration of 20 to 25 gr. of sodium bicarbonate, in addition to the diet, brought about this desired end. The success of such dietary treatment of epilepsy in children appears striking from a survey of the author's data. Of 37 patients treated, 19 have been entirely free from attacks for periods ranging from three months to two and a half years. Several patients have had attacks only following breaks in the diet, usually carbohydrate indulgence. Thirteen patients were definitely improved and 12 of these are still undergoing dietary adjustment to further control the convulsions. Three were free from convulsions for three to eight months and were then lost sight of. One made no improvement and 1 is still early in treatment. In some cases the high fat diet is not well tolerated by the patient, especially if started too abruptly. The nausea and vomiting sometimes occurring at the start are readily relieved by orange juice. Carbohydrate must be avoided so far as possible, however, because it is just this lack of glucose oxidation that brings on the desired ketosis.

SURGERY

UNDER THE CHARGE OF

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Polyposis of the Colon.—ERDMANN and MORRIS (*Surg., Gyn. and Obst.*, 1925, 40, 460) state that the term polyposis of the colon is used to designate an adenomatous hyperplasia of the intestinal mucous membrane as opposed to those polypoid tumors of the intestines which are histologically fibromata, myomata, etc. Polyposis of the colon appears to be a uniform, nonspecific mucous membrane reaction to a chronic irritant in the presence of a preternaturally sensitive mucous membrane. It is manifested grossly as scattered intraluminary tumors, varying in size from a split pea to a grape-fruit and has a specific predilection for the large gut and rectum. This predilection increases as we proceed from the ileocecal valve. Two clinical types may be distinguished—an adolescent variety in early youth with recurring attacks of intestinal hemorrhage and diarrhea and showing a distinct tendency to involve members of the same family, and an acquired variety first appearing in

adult life in association with frank evidences of chronic traumatic and inflammatory lesions to which they are evidently secondary. The two types have in common the marked predilection for the large gut, a malignancy incidence of more than 40 per cent and a tendency to chronic intestinal hemorrhage and diarrhea. They are dissimilar in that the adolescent type is widely disseminated, appears in almost countless numbers and shows no gross evidence of a causative lesion, while the adult type occurs in limited number and is almost invariably associated with gross evidence of trauma, inflammation or foreign body. Indications for treatment are the depleting hemorrhage, diarrhea and the high malignancy incidence. Nonradical palliative treatment comprises cecostomy, irrigations and radium therapy. Radical effective treatment, excision of the polyp-bearing area is limited by technical difficulties and the inability to predict preoperatively the extent of the process.

Tannic Acid in Treatment of Burns.—DAVIDSON (*Surg., Gynec. and Obst.*, 1925, 41, 202) states that the preliminary treatment of burns with tannic acid compresses followed by exposure to air lessens toxemia. After coagulation of the devitalized tissue with tannic acid the application of a wet boric acid dressing apparently causes a return of toxic symptoms. Tannic acid as an initial dressing on a burn is analgesic. The subsequent use of the open air method causes minimal trauma and promotes general comfort. The local astringent effect prevents the loss of body fluid. Secondary infection is markedly limited by the absence of a favorable nidus for bacterial growth. Scar tissue formation has been less marked than that observed after treatment by other methods. The protective layer of coagulated protein forms a scaffold for the growth of the young epithelial cells over the denuded surface.

Cystic Inflammation of the Vesical Neck and of the Prostatic Urethra.—LAZURUS (*Surg., Gynec. and Obst.*, 1925, 41, 162) claims that cysts and polypi around the internal vesical sphincter and in the prostatic urethra are frequently secondary to specific and nonspecific prostatitis. Such cysts and polypi can attain very large dimensions and be mistaken for neoplasms. The lesions in this condition differ from those in cystitis cystica in that they never invade the bladder and are of a purely inflammatory nature. A combination of fulguration of the cysts and of local treatment for the prostatic condition will always yield excellent results in these cases.

The Residual Paralysis and Deformity of Anterior Poliomyelitis.—MITCHELL (*Jour. Bone and Joint Surg.*, 1925, 7, 619) says that anterior poliomyelitis is an infectious disease characterized by inflammation of the gray substance of the spinal cord and attended by motor paralysis and deformity. It is of wide distribution and often occurs in epidemics. Experiments have shown that the infecting organisms enter the body probably through the upper respiratory passages. In this series the disease occurred during the first three years of life in 44 per cent of the patients. The onset is acute, but the residual state of deformity is permanent and may progress or become accentuated by

the growth of the child. Usually the patient does not seek aid until after the deformity has become well established. The average duration of the paralysis in a series of 350 cases was eight and three-fourths years. The paralysis is most marked in the lower extremities. The anterior tibial muscle was the one most commonly paralyzed. Talipes equinus and talipes vulgus were the most common deformities. Scoliosis occurred in 31.4 per cent of the cases. Marked improvement follows proper treatment given early in the disease. The treatment consists of rest, massage, the applications of heat, muscle training and the use of splints and braces. In many cases surgical treatment of the residual deformity is of great benefit. It aids in correcting deformities, stabilizing the limb and increasing the function of the limb.

Abnormal Arteriovenous Communications, Acquired and Congenital.—REID (*Arch. Surg.*, 1925, 11, 25) says that an arteriovenous fistula is a powerful stimulus to the development of a collateral circulation, much greater even than is the stimulus of ligating the vessels. A fistula between artery and vein leads to marked changes in the vessels. The arteries proximal to the fistula become dilated and thin-walled and often show marked degenerative changes. A true aneurysm may form in an artery proximal to the fistula. The veins dilate and their walls may become thickened. A fistula between large vessels may lead to grave cardiac disturbances or even to sudden death. The circulation of a limb distal to a fistula is usually markedly impaired, even though there is an increase in the capillary bed. The surface temperature distal to a fistula is lowered, while after extirpation of the fistula it may be several degrees higher than it is normally. Arteriovenous or cirsoid aneurysms situated in the extremity of a growing individual may cause a considerable increase in the length of that extremity. In the author's experiments a kidney does not live after a complete reversal of its circulation.

Perinephritic Abscess in Children.—PUGH (*Urol. and Cutan. Rev.*, 1925, 7, 387) writes that perinephritic abscess, particularly that due to metastases is more common than generally supposed. The history of an infection and pain in the costovertebral angle in children should arouse suspicion. All cases are not so clear cut as those in this series and should be given the benefit of a complete urologic examination if possible. An exploratory operation is justifiable in doubt. Surgery in this class of cases can and should be done under local anesthesia. Experience has convinced the authors of the great prevalence of urological manifestations in children and the field opened by modern technics.

A Basis for Comparing Results in the Treatment of Ureteral Calculi.—HAHN (*Am. Jour. Surg.*, 1925, 39, 161) states that cystoscopic findings were positive in 97 per cent of the cases. These positive findings in order of frequency are as follows: Diminished excretion of indigocarmine by one kidney, partial obstruction of ureter, complete obstruction of ureter, scratch mark on wax-tipped bougie, no excretion of indigocarmine by one kidney, stone seen at ureteral orifice, stone seen in bladder, ecchymosis and edema near ureteral orifice and

grating sound or sensation upon passing ureteral catheter. In 4 cystoscopically negative cases there were positive roentgenograms, and in 2 red blood cells in the urine previous to cystoscopy. The roentgen ray misses 17 per cent of ureteral stones. In a series of 147 cases positively diagnosed as ureteral stones 17 per cent of the stones were passed spontaneously before cystoscopy; 15 per cent of the stones were passed at or following cystoscopy; 37 per cent of the stones required operative removal; 30 per cent of the patients were treated conservatively. Of the cases in which the stone was not passed spontaneously, and could not be induced to pass by a reasonable trial of cystoscopic methods, 55 per cent required operative removal.

Periarterial Sympathectomy.—BERNHEIM (*Surg., Gynec. and Obst.*, 1925, 40, 828) states that the so-called periarterial sympathectomy of Leriche is a procedure that may be of great usefulness in the prevention and relief of circulatory disorders of the extremities that are wont to eventuate in gangrene. The operation consists essentially in the elimination of sympathetic nerve control over certain bloodvessels, as a result of which they are permitted to dilate and carry apparently a greater quantity of blood than they had been carrying. Exact indications for its use remain somewhat problematical but certain states characterized by a spastic condition of the bloodvessels offers its greatest field. Nothing is to be hoped for in arteries completely thrombosed, and at the present time the arteriosclerotic disorders, diabetic and syphilitic, do not seem amenable to relief in this manner. The operation itself, while not simple or devoid of danger is not too difficult and any surgeon of experience should be able to do it satisfactorily. The chief point of importance is to secure absolute removal of the adventitial coat of the artery, since the sympathetic nerve fibers are for the most part in this coat and the purpose of the operation is their removal.

Tuberculosis of the Tongue.—FINNEY and FINNEY (*Surg., Gynec. and Obst.*, 1925, 40, 743) claim that there were only 2 cases in women among 15 cases. Direct trauma seems to be the only important causative factor in any of these cases. In no case was the trauma to be charged to that popular bugbear, the pipestem. Pain is not a prominent feature in this list of cases. In only 1 case was pain of the excruciating character usually described. There is no site of predilection for the development of the lesion. Any portion of the tongue may be attacked with most of the lesions occurring anterior to the circumvallate papillæ and about equally divided between tip, margins and dorsum. The tongue lesions may be single or multiple. There may or not be any regional adenopathy. The authors have no special form of treatment to advocate. It would seem wise, however, in a case which seems to be primary to treat it by wide excision, much as if it were carcinoma.

Preoperative Skin Disinfectant.—SCOTT and HILL (*Jour. Urol.*, 1925, 14, 135) state that the alcohol-acetone-aqueous solution of mercurochrome which is made by dissolving 2 gm. of mercurochrome in 35 cc. of distilled water, and then adding 55 cc. of 95 per cent alcohol and 10 cc. of acetone, is a very efficient preoperative skin disinfectant.

Better skin sterilization is obtained with it than with iodine, "kalmerid" and picric acid. Its application is accompanied by no pain, and it is therefore of special value in cases operated upon under local anesthesia. Regardless of the age of the patient or location of the operative field, no instances of dermatitis have occurred following its use in the authors' series. This solution penetrates at least as deeply as picric acid and seems to be a little more uniformly distributed at its lower level of penetration. It retains high bactericidal properties at least for forty-six days, as shown by controlled experiments upon a rabbit skin heavily inoculated with *Staphylococcus aureus*. It has a relatively low toxicity, as shown by the vigorous way that tissue cultures and transplants have grown after its use.

PEDIATRICS

UNDER THE CHARGE OF

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Control of Rickets.—ELIOT (*Jour. Am. Med. Assn.*, 1925, 85, 656) remarks on the extraordinary chronicity of rickets in his series of roentgenograms. The evidence of rickets first seen in the second or third month of life may be followed month after month even to the end of the first year or later. If the infant is under treatment evidence of lime salt deposit as well as the evidence of active rickets may be seen. The process finally becomes low grade and sluggish, and though constantly present is controlled. If the infant is not under treatment the roentgenogram shows increasing and accumulating evidence of the disease month after month, until the well-known picture of marked rickets is seen. Lime salts apparently can be deposited in one part of the cartilage of a growing bone, when they are not deposited in other parts. Rickets and the repair of the rachitic process go on hand in hand for months, and in some instances for years. That rickets is intimately associated with growth is well known, and that it should appear at the time when most active growth is taking place, namely, the first four months of life, is not extraordinary. Large, rapidly growing breast-fed babies and very fat infants uniformly show definite evidence of rickets. It is an uncommon thing to find a healthy vigorous baby although breast fed who does not show rickets by roentgen-ray examination. Premature babies who grow exceedingly rapidly are notoriously rachitic. Malnourished infants frequently show small, slender bones with little or no rachitic change. If any two groups of infants show need of early antirachitic treatment more than the others they are the large, rapidly growing breast-fed infants and premature infants. The investigations showed that a slight degree of early rickets is almost universal in our climate and in our state of society. The very intimate association of rickets with growth, its

early appearance regardless of season and its universality engenders the question, whether this slight degree of rickets must be considered normal. The author is not prepared to answer this question at this time. Before an answer can be accurately arrived at it would be necessary to study the amount of rickets existing in a group of infants born and living in the tropics. _____

Static Peritonitis in Malnourished Infants.—FOOTE (*Jour. Am. Med. Assn.*, 1925, 85, 720) says that premature, toxic and typically athreptic infants display symptoms of peritoneal injury in a manner that may be termed static. One of these patients showed infection through the umbilical vein. In intussusception in the athreptic infant pain, tumor and vomiting may only be seen late in the disease, and diagnosis may be difficult. Even slight distention, not reducible by enemas in emaciated infants, should be contraindicated for intraperitoneal instillation of salt solution or of blood. A gain in weight after this procedure in desperately-ill athreptic patients means a nonabsorbing peritoneum. Usually by the time that it is possible to establish the diagnosis with certainty treatment is unavailing. Hence the need for prophylaxis of athrepsia by breast-milk feeding and care as to the hygiene of the infants in the first weeks of life. The use of pituitary extract to promote peristalsis in young infants is fraught with danger, since it readily produces intussusception. In defining the hypothreptic infant, Marfan speaks of those infants who have not passed the threshold of actual atrophy, and he describes as athreptic those who show the characteristic syndrome. This syndrome is ordinarily caused by food injuries plus acute infections, such as pharyngitis. Chronic or subacute infections, such as tuberculosis, syphilis, or the terminal stage of such acute infections as are produced by the less virulent types of the dysentery group of bacteria, may also be the provoking agents of the metabolic disturbance. The apparent functional disability of alimentation, as shown by defective digestion and absorption, has in the past been attributed to the impaired nutrition of the intestinal glands and of the intestinal mucosa and the muscularis.

Does Roentgen Ray Modify the Course of Whooping Cough?—FABER and STRUBLE (*Jour. Am. Med. Assn.*, 1925, 85, 815) report the results of a study based upon equal numbers of control and test cases, selected in such a manner as to afford if possible a just comparison between those treated and those not treated with the roentgen ray. Forty-four consecutive cases in the paroxysmal stage of pertussis formed the material for this study. Twenty-two of these were given treatment by roentgen ray and the remaining 22 were treated with antipyrin. With 5 exceptions, the division of patients into the two groups was by alternation. Of the 5 exceptions, 2 patients were suffering from a rather severe form of the disease, their inclusion has raised the average number of paroxysms and perhaps the average duration of the disease in the irradiated group. It may have been better not to have treated the control group at all, or perhaps with a placebo. This was not done, as it did not seem right to leave the children untreated, so moderate doses of antipyrin were given. The irradiated patients were also given the same drug when it was evident that no effect was being

obtained from the roentgen ray. The two groups, therefore, afford a comparison between children treated with antipyrin and children treated with roentgen ray plus antipyrin in some cases. The diagnosis was made on characteristic symptoms, and in most instances was corroborated by blood count. Cultures were not taken. Mothers were required to make daily notation of the number of paroxysms, which were defined as a coughing spell followed by a definite whoop, and of vomiting attacks. These reports were brought to the clinic once a week. After the disappearance of the whoop reports were continued for some time. Delinquents were followed. The roentgen-ray treatments were uniform, according to the following specifications: Eight milliampères, 9-inch parallel spark, 0.25-mm. copper and 1-mm. aluminum filters, 12-inch anode skin distance to 6-inch circular areas front and back of the chest. Treatments were graduated by age periods, and were given on the first fourth and eighth days of observation. These observers found that the disease ran an average longer course, fewer patients ceased whooping in the early weeks and more patients were whooping in the later weeks in the irradiated series than in the controls. This study would appear to justify the conclusion that roentgenotherapy is without true beneficial effect in pertussis. The method used here did not differ in essentials from that used by others. It may be that occasional temporary exacerbations or inhibitions may occur shortly after roentgen-ray treatment, but these should probably be ascribed to psychic disturbances. Effects of greater extent or duration, such as have been previously reported from roentgen ray, as from other modes of treatment, are in all probability apparent rather than real, and represent normal fluctuations in the course of a highly variable disease.

Universalizing Breast Feeding in a Community.—RICHARDSON (*Jour. Am. Med. Assn.*, 1925, 85, 668) gives the three essentials for accomplishing this procedure: (1) There must be a group of physicians who are convinced of the overwhelming superiority of breast feeding over bottle feeding, who believe that it is attainable for the vast majority of infants, and who are familiar with a working technic for making breast feeding possible for the individual child; it is well known that the main points of this technic are the manual expression of the mother's breasts after nursing and the giving of complimentary feedings whenever the amount of breast milk secreted is insufficient, the amount taken to be judged from the desire of the infant. (2) There must be coöperation of the birth-recording department or bureau of the community. (3) There must be an organization controlling sufficient nurses trained in the technic of breast feeding visit each new mother as soon as a birth certificate is filed, in order to instruct her in the desirability of keeping the baby on the breast, as well as in the way to accomplish this. They found that nine-tenths of the mothers succeeded in nursing their babies for one month, and that two-thirds of them did so for seven months. The infant mortality rate of the 2815 babies studied was 49 per 1000. That of the county for the year of the campaign was 64. The mortality rate for the three previous years averaged 72. The morbidity of children nine months breast fed, as compared with that of children less than nine months breast

fed, was said to effect, as would be supposed, diseases of the digestive tract, where the ratio was almost 3 to 1 in favor of breast feeding. Respiratory diseases showed the next highest variation. Pneumonia and bronchitis was very prevalent in the children with limited breast feeding. These children were also susceptible to infectious diseases, especially whooping cough, measles and chicken pox. One-third of the children prematurely weaned became sick as over against one-eighth of those who were breast fed for nine months.

GYNECOLOGY

UNDER THE CHARGE OF

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Bilateral Urethral Implantation.—The subject of ureteral implantation must be of interest to every gynecologist, since there are occasions, either accidental or intentional, when it is necessary to perform such a procedure, and only when such an operation is performed by a perfected technic can favorable results be expected. For many years this subject has been investigated by COFFEY (*Northwest Med.*, 1925, 24, 211) who has recently made another contribution in this field. Being interested in the radical cure of carcinoma of the bladder and in the relief of inoperable carcinoma, he realized that diversion of the kidney function was the first essential to success in either case. He discovered experimentally that both ureters could not be transplanted at the same time, for the reason that there seemed to be a postoperative edema in the intestinal wall which was sufficient to obstruct the lumen of the ureter and thus temporarily destroy kidney function. Animals in which both ureters were transplanted died. When one ureter was transplanted the urine would not come into the intestine for from three to eight days and then the kidney would begin to function in a normal way, and it has been found necessary to permit the first kidney to have sufficient time to recover its function before the second ureter is transplanted. Removal of the bladder then meant a third operation. Patients of the cancer age usually have a diminished kidney function and diminished resistance in other respects, therefore the ordeal of three operations have seemed so formidable that few have had the temerity to use it in cancer. Another drawback has been that the ureters are frequently dilated from back pressure when the patient comes to the surgeon. The improved technic which he is now using consists of opening the abdomen near the median line. A rectal tube is passed up into the pelvic colon to a point where it is desirable to implant the left ureter. This

tube drains away all gas and any possible fecal matter which may be present and makes the use of clamps unnecessary. The left ureter is exposed and ligated between forceps. The distal end is cauterized with carbolic acid and dropped back. Into the proximal end is fastened a very small rubber tube, 2 or more feet in length. This is done by passing a small straight needle armed with linen through the wall of the ureter and including barely enough of the tube to hold. Then the thread is tied around both the tube and ureter sufficiently tight to control the urine and later to cause sloughing of the tied end. The right ureter is then treated in the same manner. It will be found that the urine is discharging through both of these tubes. Next the intestine on the left side is lifted at a point where the ureter may be inserted without tension or strain. Gauze is packed on either side of the intestine so that any possible leakage from the intestine will be caught. An incision about $1\frac{1}{2}$ inches long is made near the center of the free margin of the largest intestine and made to curve over to the outer side. This incision goes through the peritoneum and muscle, and the mucosa is carefully freed from the muscularis, allowing the mucosa to pouch out through the incision in the muscular wall. The same is performed lower down the intestine on the right side. A small stab wound is made through the mucosa at the lower angle of the intestinal wound and the end of the small rubber tube is attached by a linen suture to the end of the rectal tube. On the right side a small incision is made in the mucosa and the end of the right ureteral tube is attached to the side of the rectal tube. A nurse then pulls down on the rectal tube and draws the two ureteral tubes down until the ends of the ureters are drawn well within the lumen of the intestine. The ureters containing the tubes now lie directly on and outside of the loose mucosa of the intestine. The wall of the intestine on either side of the cut, forming the two lips of the wound, is drawn across the ureter and some of the sutures are made to penetrate the outer coat of the ureter. These sutures should be of interrupted chromic catgut. Finally a continuous catgut suture should roll the serous coat over the line of incision, thus reinforcing it, and the abdomen is then closed. The tubes protruding from the rectum are placed in a container for the urine. The kidneys function without even temporary cessation. The tubes come away in about a week, the swelling in the intestinal wall has subsided and the implantation is complete. By the use of the tube to transmit the urine through the edematous tissues surrounding the anastomosis, the kidney functions just as if the ureter were brought out through a loin wound, therefore both ureters may be implanted simultaneously with impunity, and it may even be possible to remove the bladder at the same sitting, but, as a rule, this had better be deferred until a later time.

Autotransfusion in Ruptured Tubal Pregnancy.—In the tragic type of ruptured tubal pregnancy the successful outcome of surgical operation often depends on the quick replacement of the blood lost. This is usually accomplished by means of blood transfusion, but very often valuable time is lost in securing a donor of the proper type. In order to overcome this difficulty, autotransfusion, or recovery of the blood in the peritoneal cavity and reinjecting it into the patient's vein, has

been suggested as a valuable procedure, and a report on the use of this method in 26 patients has been presented by HEMPEL (*Zentralbl. f. Gynäk.*, 1925, 49, 407). Of this series there was 1 death of a patient who was moribund and who died on the table. The author begins the operation by giving an intravenous infusion of normal saline solution. After the solution is flowing freely in the vein the abdominal incision is made. A small midline incision is made and the peritoneal edges are drawn upward so that very little of the blood in the peritoneal cavity can escape through the incision. The contained blood is scooped out of the peritoneal cavity, strained and mixed with sodium citrate solution and then placed in the container which holds the saline solution, which should be kept warm throughout the procedure. The abdominal incision is then enlarged and the remaining blood is scooped out, obtaining as much as possible by changing the position of the table and by milking the blood from the flanks. As quickly as possible, without losing too much blood, the diseased tube is clamped and removed. The condition of the patient is usually so much improved by means of the transfusion that the remainder of the operation proceeds in an orderly fashion with little danger. By means of this autotransfusion it is often possible to return to the patient's circulation from 1000 to 2000 cc. or more of blood. Whereas formerly it was obligatory to perform these operations in fifteen minutes, by means of this technic the patient is usually able to withstand careful removal of both tubes if advisable and even appendectomy. Since ectopic pregnancy recurs in from 5 to 9 per cent of cases, Hempel believes it is advisable to remove the opposite tube if the patient has children and is not anxious to have more.

The Cancer Problem.—As on several previous occasions, it is again our privilege to call attention to some of the conclusions of HOFFMAN (*Pub. Health Jour.*, 1925, 16, 256), one of our best-known cancer statisticians, which have been reached as a result of his recent survey in San Francisco. His investigation concerning living cancer patients clearly proves that there has been on an average a loss in weight of about 30 pounds between the onset and the termination of the disease. General indications are that most of the patients, while in good health, were above the average weight in proportion to their height. Many of them frankly admit themselves to be heavy eaters, particularly heavy meat eaters and heavy sugar eaters, while only a small proportion of the patients were heavy fat eaters. In about one-half of the cases there is an admission of a chronic condition of intestinal stasis and of the habitual use of purgatives or laxatives. In about one-third of the cases the patients suffer, or have suffered, from rheumatism or a chronic rheumatic condition. The evidence regarding heredity was practically negative. The argument frequently proposed that many of the cancer patients of large cities are nonresidents is clearly disproven by the San Francisco investigation. The average duration of residence had been twenty-two years in San Francisco and thirty-three years in California. The sum and substance of the problem may be summed up in the statement that the principal cause of cancer mortality is delay on the part of the patient to seek qualified treatment. The appalling mortality from cancer admits that a cure for the disease, in

the technical sense of the term, has not been discovered, but it would be unfair to the medical and surgical profession, states the author, if attention were not drawn, to an increasing extent, to successful forms of control, but for which the cancer death toll would reach, even ordinarily, more alarming proportions. Anyone familiar with hospital or private medical and surgical experience knows full well that thousands and tens of thousands of persons who have been operated on for cancer are alive and well today. It is regrettable that the collective experience in this respect should not have long since been brought together as an unanswerable argument of the dictum that in the earliest qualified treatment lies the only hope of cure.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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Psychic Manifestations in Cases of Brain Tumors.—MOERSCH (*Am. Jour. Psychiat.*, 1925, 81, 705) found that of 239 cases of brain tumor at the Mayo Clinic 73 had definite mental changes. A high percentage of unilateral frontal or corpus callosum tumors showed such changes. All callosal tumors were in this group. The author groups the psychic symptoms of brain tumors under three headings: (1) General symptoms, such as mild mental and physical let down (neurasthenic states); mild changes in personality (indifference, inadequacy, "witzelsucht"); anxiety states; depressive reactions; mental confusion; deteriorating states simulating epilepsy, arteriosclerosis, senile dementia, vascular lesions, traumatic lesions, dementia paralytica, dementia precox (catatonic states); these have no localizing value according to the author. (2) Specific mental reactions, such as lack of effect (change in personality); impaired mental grasp (lack of memory, interest and attention); impaired insight and judgment; impaired mental activity (poverty of thought processes); disturbances of general motility (psychosomatic); in the absence of localizing signs these constitute what the author calls a frontal lobe syndrome, meaning that it is not positive, but suggestive. (3) Associated mental reactions, such as hysterical episodes, maniacal states, or other psychotic states which may be quite independent of the effects of the neoplasm and are usually seen in neuropathic individuals. Seven tumor case histories are given to illustrate symptoms and lesions in various parts of the brain.

A Review of Some Studies of Delinquents and Delinquency.—HEALY (*Arch. Neurol. and Psychiat.*, 1925, 14, 25) reviews 4000 cases of delinquency in children of average age, fourteen to fifteen years, half of whom were in Boston and half in Chicago. Over development, especially in girls, seemed to be the rule. Premature puberty occurred

in 10 per cent, delayed puberty in 3 per cent. Sensory defects were not unusual in frequency. The most common organic nervous disease was chorea. The author feels that the whole group has a greater incidence of head traumata than the normal. Congenital syphilis was relatively rare. The so-called stigmata of degeneration were present in 6 per cent. Goiter was many times more frequent in the Chicago group. Definite feeble mindedness was present in 13.5 per cent of the total group. More of the Chicago group had psychoses (5.6 per cent to 1.1 per cent). Epilepsy was present in 5.5 per cent of the Chicago group and in 1.8 per cent of the Boston group. The author cites the result of 127 mentally abnormal boys who were in need of special care but did not receive it. Ninety-three of them committed desperate acts and were the source of great expense to the state.

Extensive Brain Hemorrhage.—WINKELMAN and ECKEL (*Jour. Nerv. and Ment. Dis.*, 1925, 61, 593) report briefly 30 cases of cerebral hemorrhage. In 22 the hemorrhage had broken into the ventricles, and in these cases death occurred from five hours to fifteen days after onset. Convulsions occurred in only 2 cases. Consciousness was lost soon after the onset in 23 of the 30 and was altered in 4 others. One case of hemorrhage into the pons was fatal in an hour. The authors conclude that cerebral hemorrhage and even pontine hemorrhage is not a cause of immediate death.

Mental Examinations of College Men.—PECK (*Am. Jour. Psychiat.*, 1925, 4, 605), in a review of 59 students at Harvard considered 22 normal, 14 had minor personality defects, 20 were neurotic and 3 psychotic. They were classified roughly according to Jung's classification of extraversion and introversion. Extraverts predominated. Case histories are given illustrating both introverts and extraverts, with varying degrees of personality defect. The writer feels that there is a very definite need for psychiatric examinations among college men as a prophylactic and therapeutic measure.

The Relation of Intelligence to the Etiology of Drug Addiction.—KOLB (*Am. Jour. Psychiat.*, 1925, 5, 163) cited two surveys (Boston and New York) from which it was concluded that more drug addicts are mentally deficient than is found in normal social groups. In the writer's group of 100, composed of colored and white, and in which he did not place some higher grade professional individuals who were addicted, there were 10 with intelligence quotient below 70; 10 with intelligence quotient between 70 and 75; 14 between 76 and 85; 38 between 86 and 95; 20 between 96 and 105; 7 between 106 and 110; 1 over 110. There were 25 colored people included in this group. The writer feels that the Stanford-Binet test is not a fair measure for adults. The basis of drug addiction is thought to be a neurotic or psychopathic personality which is only indirectly related to any defect of intelligence.

Negative Histologic Findings in Experimental Organic Processes.—ORTON (*Am. Jour. Psychiat.*, 1925, 4, 599) states that death was induced in experimental animals by methods which obviously impli-

cate the central nervous system. In the first group of 5 animals both carotid arteries were suddenly ligated and 3 of them promptly had convulsions. In the second group of 8 dogs tetany parathyreopriva was induced, and the animals were killed in various stages of the disease. In the third group animals died in convulsions from acute oxalic acid poisoning. In the fourth group animals were allowed to develop convulsions from an overdose of insulin, or were caused to have convulsions from moderate doses of insulin over a period of time. In all groups careful histologic studies were made of the brain. Some variations in histologic structure were observed, but nothing was found which could not occasionally be seen in the controls. The writer justly concludes that if no constant structural changes can be demonstrated in animals that died obvious cerebral deaths, we are far from being able to ignore the organic possibilities of some of the psychoses, even though no pathologic variations are demonstrated.

Epidemic Encephalitis.—The various methods of treatment of this disease are mentioned and referred to in the bibliography. STRECKER and WILLEY (*Am. Jour. Psychiat.*, 1925, 4, 631) treated 14 patients with sequels of encephalitis by intravenous injection of 10 cc. of 0.5 per cent neutral acriflavin. The average time from the onset of the disease until treatment was begun was three years and four months. They report marked improvement in 3 cases; some improvement in 7 others; very little or no improvement in 4. A table is given showing the condition of patients before and after treatment. In 2 cases pregnancy went to term with delivery of healthy children while the patients suffered from the sequels. In 2 other cases the onset of the disease was soon after childbirth. The authors are hopeful that this method of treatment may be as helpful in other cases as in their own.

The Use of Lipiodol in Tumor of the Spinal Cord.—MIXTER (*Arch. Neurol. and Psychiat.*, 1925, 14, 35) reports the results of lipiodol injection for the diagnosis of cord tumors in 12 cases. When injected into the lumbar sac, and the patient placed in the Trendelenberg position, the oil gravitated poorly toward the head. A meningeal reaction reached its height in twenty-four to forty-eight hours following the injections. In some cases the cell count reached 1000 and the fluid even became slightly turbid at the height of the reaction. Lipiodol apparently has remained unchanged in the spinal canal eight months after injection. The appearance of an oily cap in the roentgenograms in the region of a suspected tumor seemed to be confirmatory evidence. The author cites the work of the French and brings up the criticism that lipiodol may not be of value in cases of tumor without block. As with all diagnostic procedures, lipiodol should not be relied on solely, but should assist where physical diagnosis has been carefully done.

Aseptic Meningitis in the Treatment of Dementia Praecox.—CARROLL, BARR, BARRY and MATZKE (*Am. Jour. Psychiat.*, 1925, 4, 673) state that it has been known for years that some cases of dementia praecox improve temporarily while reacting to an acute infection or inflammatory process. Following other lines of research, especially on

aseptic methods of producing irritation in the spinal canal, Carroll injected 25 cc. of inactivated horse serum into the spinal canal of a patient in a catatonic stupor. An aseptic meningitis followed, but no mental change. The same treatment was given a week later, and the following day the patient "was quite himself for the first time since admission." Of 49 cases so treated at the Philadelphia Hospital for Mental Diseases 14 showed no improvement, 28 were improved and 7 showed remissions. A detailed account of laboratory examination of cells of spinal fluid is given. Contraindications for continuation of this treatment are failure of temperature to return to normal, or an eosinophilia of 15 per cent or more. A large number of case histories detail in a fragmentary way the status of patients before and after treatments. Within two to eleven months after producing aseptic meningitis the authors draw conclusions as to the therapeutic effect of this method of treatment. In other ways the study seems inadequately controlled.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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Fibroma of the Acoustic Nerve.—It is known that certain tumors, such as glioma, dural endothelioma and the acoustic nerve fibroma may develop at the cerebellopontile angle. CUSHING (*Tumors of the Nervus Acusticus*, Saunders, 1917) called attention to the acoustic nerve tumor as a clinical and pathologic entity, their origin usually being in the sheath of the eighth cranial nerve. Most of these neoplasms are unilateral. When bilateral they are usually an expression of a widespread affection of nerve sheaths commonly known as von Recklinghausen's disease. Clinically, the acoustic tumors, owing to the characteristic chronology of their symptoms, may, as a rule, be sharply distinguished from all other tumors of the cerebellopontile angle. According to Cushing, the symptomatic progress of the average acoustic tumors occurs more or less in the following stages: "(1) The auditory and labyrinthine manifestations; (2) the occipito-frontal pains with sub-occipital discomfort; (3) the incoördination and instability of cerebellar origin; (4) the evidences of involvement of adjacent cerebral nerves; (5) the indications of an increase in intracranial tension with a choked disc and its consequences; (6) dysarthria, dysphagia; and finally cerebellary crises and respiratory difficulties." JACOBSON (*Am. Jour. Path.*, 1925, 1, 259) adds 3 cases of cerebello-pontile angle tumors, which came to his attention at autopsy. All were females, aged forty-six, twenty-two and forty-four years, respectively, the oldest individual having bilateral tumors. Histologically, the four tumors in these 3 cases were almost identical and agreed essentially with the

descriptions of the eighth-nerve tumors as given by Cushing, Mallory, Councilman and Goodpasture. They were fibromas with, however, slight deviation from the staining reactions of fibroblasts in tumors elsewhere. Their origin was apparently from the perineurium of the acoustic nerve, and they had many points of resemblance to peripheral neurofibromata. A regimental or palisade arrangement of nuclei was practically always present in some degree. The so-called reticular tissue, the author concludes, was probably the result of degeneration due to hemorrhage or thrombosis or other vascular injury. He quotes Cushing as giving the incidence of acoustic tumors in 1035 verified brain tumors as 91, or 8.8 per cent.

Abnormal Development of the Nasal Cavity of Dogs Due to Interruption of the Respiratory Current.—As only one incompletely reported experiment on the influence of the respiratory current on the growth of the nose was found in the literature, CONGDON (*Proc. Soc. Exper. Biol. and Med.*, 1925, 22, 566) interrupted the respiratory current on the left side of the nose of 11 freshly weaned puppies by introducing cotton through a window out at the dorsal end of the hard palate. The packing was changed daily and the experiment continued in most of the series for forty-six days. In 6 dogs the conchæ showed markedly incomplete development on the operated side, leaving a wide open space adjoining the septum. The usual marked curvature of the conchæ was almost completely lacking. The septum was slightly concave on the operated side, and the frontal sinus on the average was slightly larger. Histologically, no difference on the two sides was demonstrated with certainty. There was no unusual asymmetry of the face. A perfect contrast of the condition as to air circulation on the opposite side was prevented by a pressure atrophy of the septum, allowing the packing to extend somewhat over onto the unoperated side, which may explain the negative outcome in 5 of the animals. The author considered three possible factors in bringing about the arrest of development, namely, infection, stoppage of drainage and the elimination of the physical effects of the air current, chief among which are fluctuations of pressure, temperature and moisture. The evidence, as a whole, pointed to the physical effects of the air current as the cause of the abnormal development.

Studies on Pneumonia following Nasopharyngeal Injections of Oil.—It has long been customary in many children's hospitals, among pediatricians and rhinologists in private practice, to treat nose and throat infections by the use of drops of menthol and albolin or by the use of argyrol drops. This treatment, while not always beneficial, has been regarded as more or less harmless. In the routine study of autopsy material in a large pediatric institution, LAUGHLIN (*Am. Jour. Path.*, 1925, 1, 407) encountered an unusual microscopic picture in the sections of the lung from a pneumonia case, wherein large vacuolated "oil-containing" mononuclear cells were found in the consolidated portions of the bronchopneumonic process. He was able to collect 5 cases in all—4 in children and 1 in an adult, aged thirty-seven years. Three of the children had received drops of menthol (1 gr.) in albolene (1 oz.) into the nose over varying periods of time. The fourth child

had received, while in a diabetic stupor, 2 drams of paraffine oil by mouth as a laxative, while the adult, who had paralysis of the soft palate, vocal cords and accessory muscles of larynx, had been given 1.5 oz. of liquid paraffine by mouth three times a day over a period of four and one-half months, also as a laxative. In each instance certain portions of the pneumonic exudate showed the peculiar oil-laden endothelial cells. In order to explain the source of the oil and the route by which it reached the pulmonary alveoli, as well as to prove that oil would produce such reaction in the lungs of animals, several experiments were performed on rabbits, administering the menthol-albolene mixture in various ways. It was learned that the oil found its way into the alveoli of the lung, not only when directly introduced into the trachea but also at times when given in sufficient quantity in the nose and throat. In the experiments where oil was administered by mouth as well as in the clinical cases the reactions to oil were complicated by septic pneumonia, but when the oil was injected by needle into the rabbit's trachea a purely endothelial-cell reaction resulted. In the lung the oil was actively phagocytized by endothelial cells, which were present in sufficient numbers to dispose of all the oil present and produce consolidation of the lung. On the other hand, argyrol when given by mouth or introduced into the trachea, did not lead to any reaction on the part of the endothelial phagocytes in the lung.

RETROSPECTOR'S COMMENT: These are very interesting and instructive observations. In the light of these findings should not one consider more seriously not only the promiscuous use of mineral oil in the nose and throat, but also the intratracheal instillation of similar substances?

Studies on Fusiform Bacilli and Spirochetes: Occurrence in Putrid Ethmoiditis.—It has been demonstrated by Davis, Pilot, Pearlman, Brams and others that the fusiform bacillus and the associated spirochetes are important etiologic factors in putrid and necrotic lesions; that in the mouth, where they normally reside, they are responsible for certain types of foul pyorrhœa, ulcerative stomatitis and typical Vincent's angina; that like the streptococci and other pyogenic bacteria in the mouth and oropharynx, they may extend into the middle ear and give rise to the fetid discharges in chronic otitis media. More recently PILOT and LEDERER (*Ann. Otol., Rhinol. and Laryngol.*, 1925, 34, 366) reported the occurrence of these anaërobic microorganisms in 2 patients with putrid ethmoiditis. In 1 case the fusospirillary forms were recovered at autopsy from a thick pus in the ethmoid cells of a female with syphilis. In the second case, a female, aged twenty-six years, the fusiform bacilli and spirochetes were found in the expectorated material and in the ethmoidal pus encountered at operation. After twelve doses of neoarsphenamin the odor, secretion and crusting had entirely disappeared. The striking characteristic of the infection of the ethmoid cells in both instances was the foul character of the pus. In this respect sinus infection with these organisms resembled in their behavior the putrid processes observed about the mouth and in the lungs. In most of these infections the sources of infection are those organisms found normally about teeth, tonsils and in the nasopharynx. In the tartar of teeth they are constantly found. In the

tonsils bacilli occur in 82 per cent and spirochetes are particularly numerous in the granular actinomyces-like masses. In the adenoids the bacilli were observed in 32.6 per cent and spirochetes in 5 per cent. The discharge from typical cases of ozena was examined in several instances, with negative results.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Staphylococci from the Liver, Gall-bladder and Intestine of Normal Dogs.—ARNOLD, BALTHAZAR and DRAGO (*Jour. Infect. Dis.*, 1925, 36, 413) have studied the bacteria in the cystic bile and mucosa and their relation to the bacteria in the duodenum of healthy dogs. An attempt was also made to classify staphylococci from the liver, cystic mucosa and duodenum of healthy dogs on the basis of fermentation reactions and effect on gelatin, nitrates and milk in order to determine the possible source of gall-bladder strains. A series of 63 apparently healthy dogs was used, the cultures being taken first from the bile in the gall bladder, then from the cystic mucosa, and finally from the duodenum, all with the usual aseptic precautions. Details of the media and technic are given. In 5 of the 63 dogs the bile contained bacteria. In 44 bacteria were demonstrated in the cystic mucosa; 39 of these exhibited sterile bile. Details of the findings are reported. Selected strains from bile and mucosa were passed several times through rabbits. Following this 10 healthy dogs were selected, and the strains of the animal passages were injected, both with and without preliminary injection of Dakin's solution, but nothing remarkable was noted. Eighty-five strains of *Staphylococcus albus* were studied, recovered from the liver, gall-bladder mucosa, duodenum, mouth and colon of 27 dogs. The findings were indefinite but tended to indicate the strains of *Staphylococcus albus* recovered from the duodenum, mucosa of the gall bladder and liver were biologically more active than the others and resembled *Staphylococcus aureus* in character, though only showing white colonies. As a result of the study, the authors concluded that no relation could be determined between the bacteria in the duodenum and those in the cystic mucosa. The *Staphylococcus albus* isolated from the normal cystic mucosa of dogs was not pathogenic for dogs or rabbits.

Heat Produced by Union of Antigens with Antibodies.—A most interesting study by BAYNE-JONES (*Jour. Immunol.*, 1925, 10, 663) demonstrated that heat was produced by the union of diphtheria toxin and

antitoxin and also by the agglutination of *Bacillus typhosus* with its agglutinating serum. There were two periods of heat production in this latter reaction. The first, reaching its apex in one and one-fifth hours, was attributed to the combination of the agglutinin with the bacteria. The second, reaching its peak in five hours, was attributed to the clumping and flocculation of the bacteria and was considered analogous to the evolution of heat by the flocculation of colloids. The determination of the diphtheria toxin-antitoxin reaction was based on the union of 1 unit of diphtheria antitoxin with 1 Lf amount of toxin. This latter unit, 1 Lf, is determined by the Ramon flocculation test and includes all the affinities of the antitoxin. The author used the differential microcalorimeter of Hill and converted, by appropriate apparatus, the temperature changes to microvolts and degrees centigrade. The determinations required most delicate controls and careful measurements.

Allergic Reactions to the Hemolytic Streptococcus.—The association of streptococcus infections with various pathologic lesions remote from the site of the bacterial focus leads to the, at least logical, explanation that an allergic reaction may be responsible for the conditions. ZINSSER and GRINNELL (*Jour. Immunol.*, 1925, 10, 725) give some experiments evidently supporting this explanation. Guinea pigs could be rendered allergic (intracutaneous injections of 0.1 cc. of the streptococcus material) by the growth of streptococci in agar foci (Dochez), by treatment with streptococcus nucleoprotein (prepared by acid precipitation of antiformin solutions of streptococci), by injection of Dick filtrate, but the most regular and potent method was by the injection of the whole living bacteria. The Dick filtrate was the most potent substance for the demonstration of the reactions by skin test. The authors point out the interesting analogy between streptococcus allergy and the tuberculin reaction in that sensitization is most successful when the whole bacteria are injected and that the Dick filtrate which corresponds in manner of production to an unconcentrated O.T., without glycerin, is the most potent material for the demonstration of the allergic state by skin reaction.

Studies in Group Agglutination: The Absorption of Agglutinin in Diphasic Salmonellas.—Continuing his previous observations that in ordinary cultures of salmonella—*Bacillus ærtrycke*, *Bacillus paratyphosus* B and C and the Newport type—the bacilli exist side by side in two forms or phases sharply distinguished by their behavior in agglutination but not in other respects, ANDREWS (*Jour. Path. and Bacteriol.*, 1925, 28, 345) presents a study of the absorption test in this connection. Six types of salmonella are given careful and thorough consideration. Details are reported of the preparation of bacillary emulsions and sera in pure phase forms necessitating the testing of the agglutination of individual colonies. The proportions of group antigen in the specific phase and of specific antigen in the group phase were determined by absorption. This was, in short, contrasting the absorbing power of the specific and group phases of a given type first upon a pure monospecific and then upon a pure group serum prepared from that type. Details are also given of how the proper dose of each phase was deter-

mined by first plotting normal absorption curves. The "critical" dose, roughly corrected for the original titer of the serum was determined for graded absorptions of the ultraspecific serum, first with the specific and then with the group phase of the organism, and then for the converse absorptions of the pure group serum with the two phases. Percentage absorption graphs were plotted. An example of the data and procedure are given. It was found that the difference in absorbing power between the two phases is very great. In short, the specific phase possesses more than one hundred times the absorbing power for the specific agglutinin shown by the group phase, while the group phase is more than four hundred times as efficient as the specific phase for the absorption of group agglutinin. A comprehensive discussion of the variations in the results of different strains is followed by a discussion of the structure of the group elements of the salmonellas and suggestions on practical applications. It is shown that the question of phase is not one which can be neglected in absorption work involving diphasic organisms.

The Renal Circulation Rate in Experimental Oxalate Nephritis.—DUNN, DIBLE, JONES and McSWINEY (*Jour. Path. and Bacteriol.*, 1925, 28, 233) were prompted by the swollen and anemic appearance of the kidney in nephritis to investigate the rates of bloodflow, comparing the nephritis with the normal organs. Their method of measurement of rate of flow was to draw off the whole of the blood from a renal vein during a measured period of time by means of a syringe and needle, the animals' circulation being left otherwise intact. A marked disadvantage was the lowering of the blood pressure by the anesthetic. A description of the experiments and details of the technic are given. Nephritis was induced by intravenous injection of sodium oxalate into rabbits. Ten normal and ten nephritic animals were used. Blood-urea determinations are reported in the nephritic animals, and in some of the normal. It was found that there was a greater mean circulation through the kidneys in rabbits suffering from oxalate nephritis with urea retention than in normal animals.

Further Indirect Evidence that Anaërobes Tend to Produce Peroxid in the Presence of Oxygen.—M'LEOD and GORDON (*Jour. Path. and Bacteriol.*, 1925, 28, 147) publish a report of further work on the biologic activities of anaërobes. Pneumococcus has been shown to be a producer of H_2O_2 . This organism produces a greenish discoloration in heated blood ("chocolate") agar. The anaërobes under investigation likewise produce this change, and this is the basis for the presumption that they produce H_2O_2 . A survey of earlier work and observations is followed by a report of the effects of the addition to the media of various reagents likely to react to H_2O_2 . *Bacillus tetani* was the organism chiefly investigated, and pneumococcus was used as a control. Catalase from unheated blood and from liver extract, delayed or inhibited the green discoloration. The best results were obtained using catalase from unheated blood. Sensitivity to sulphids may have retarded the action of catalase in *Bacillus tetani* cultures. Small amounts of manganese dioxid, which could safely be added to the medium, were found to have little effect. The addition of glutathione

(a dipeptid made up of cystin and glutamic acid) which is a thermostable nitroprussid reacting substance appears to promote both growth and green discoloration. These findings are further evidence in support of H_2O_2 production by anaërobes. An excellent plate illustrates this paper.

HYGIENE AND PUBLIC HEALTH

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Recent Researches in Cancer.—GYE's researches (*Lancet*, 1925, 211, 109) have led him to look upon cancer—using the term in its widest sense—as a specific disease caused by a virus (or group of viruses). Under experimental conditions the virus alone is ineffective; a second specific factor, obtained from tumor extracts, ruptures the cell defenses and enables the virus to infect. Under natural conditions continued “irritation” of tissues sets up a state under which infection can occur. The connection between the specific factor of a tumor and an irritant remains to be investigated. Some of the relatively unimportant “irritants” are known, such as coal tar, paraffin oils, etc. The virus probably lives and multiplies in the cell and provokes the cell to continued multiplication. BARNARD (*Lancet*, 1925, 211, 117) has studied Gye's virus by special microscopic methods, and describes small bodies which may be seen and photographed.

The Epidemiological Importance of Diphtheria Carriers.—In study of 758 clinical cases of diphtheria in Baltimore, DOUL and LARA (*Am. Jour. Hyg.*, 1925, 5, 508) found that of 2799 family contacts not receiving prophylactic antitoxin 59, or 2.1 per cent, were attacked later than one and not later than thirty days following the onset of the primary case. In contrast to this, investigation has shown that in the family contacts of 1044 school carriers, estimated to number 4665, only 14 cases were reported within thirty days of the discovery of the carrier. After making necessary allowance for differences in age distribution of the two groups of contacts, it is a conservative estimate to state that the risk of attack is ten times as great for family contacts of cases as for those in similar association with known bacillus carriers. Comparison of the attack rates in families of carriers with the prevailing attack rates in the general public of the city indicates that during the first month following discovery of the carrier the attack rate in the family contacts is considerably higher than would be expected in a random sample of the city's population of the same age distribution,

whereas in subsequent months no such excess is indicated. The interpretation of the excess attack rate in carriers' families during the first month of observation is complicated by a number of considerations which are noted in the presentation of the data. Nevertheless, it seems reasonable to conclude, since the statistical observations are in agreement with many other general facts known regarding the epidemiology of diphtheria, that the families of known bacillus carriers do incur a risk of developing clinical diphtheria which, though small, is appreciably higher than that incurred by otherwise comparable families in which such carriers are not known to exist. It should be noted, however, that the evidence cited justifies this conclusion only as regards carriers discovered in schools where clinical diphtheria was prevalent at the time, for among the family contacts of chance carriers, found in a random sample of school population, there is no evidence of any greater incidence of diphtheria than that prevailing in the general population of the city. The number of carriers of this kind observed, namely 104 "virulent" and 261 "avirulent" is, however, too small to justify any sweeping conclusions regarding the risk of attack to which their family contacts are subject. This study fails to show any significant distinction between the risk of attack for those exposed respectively to carriers classified as "virulent," "avirulent" and "not tested." The fact that such are not brought out by analysis of the data presented does not, however, justify the conclusion that differences do not exist, and it may be that a study of a larger number of families would indicate that the risk of attack may vary according to the type of bacillus harbored by the carrier.

Humidity Control in Residences.—DRINKER (*Am. Jour. Pub. Health* 1925, 15, 689) states that during the months of central heating, increasing the humidity of the air permits the maintenance of lower temperatures, decreases dustiness, prevents the deterioration of plants and furnishings, and improves the atmosphere from the standpoint of health and comfort. The chief drawbacks in humidity control are: (a) Loss of moisture, initially through absorption by the contents of the residence, and constantly through air leakage; (b) condensation of moisture on cold objects, such as windows; (c) increase in fuel consumption. Mechanical humidifiers, such as sprays and centrifugal atomizers are discussed, as well as devices in which moisture is evaporated from pans on radiators, from troughs of warm air furnaces, and from the surface of wet towels or wicks. A mechanical humidifier functioning by the last method is described and illustrated. Typical performance curves are given, showing the evaporative power of these devices in different humidities and the control they effect.

Interracial Variation in Infant Mortality.—DEPORTE (*Am. Jour. Hyg.*, 1925, 5, 454) states that there has occurred in the six-year period, 1916 to 1921, a definite decline in the rate of infant mortality in all racial groups. The decline has been both absolute and relative, reducing the degree of variation between the rates of the diverse groups. The differences in the rates of infant mortality of the several groups have been due primarily to differences in the rates of mortality from diseases of the digestive and of the respiratory systems, and, therefore,

in large measure, influenced by environmental factors which are, theoretically, preventable. There has been less change, absolute and relative, in the rates of mortality of infants under one month. These deaths are brought about by causes as yet little understood, and except in the cases of premature births not likely at the present time to yield to organized public effort. The differences between the various groups in these rates very probably have a biologic basis, and in this sense may be termed racial.

The Germicidal Properties of Soap.—WALKER (*Jour. Infect. Dis.*, 1925, 37, 181) claims that soaps are not to be regarded as general germicides, but in using them for their detergent properties advantage may be taken of their germicidal activity against the streptococcus, pneumococcus, diphtheria bacillus and to a lesser extent against the typhoid bacillus. The thorough washing of the hands with the formation of a good lather will destroy any adhering diphtheria bacilli, streptococci and pneumococci. Any ordinary soap will serve for this purpose. Coconut oil soap is the only soap appreciably active against the typhoid bacillus at ordinary temperatures. In order to kill typhoid bacilli on the hands the washing should extend over a period of at least three minutes, with the formation of an exceedingly stiff lather. The use of a nail brush in washing the hands in order to render the surface under the nails accessible to the action of soap is desirable. The activity of soap is greatly enhanced by raising the temperature. This germicidal activity of soap against the typhoid bacillus seems to be due to its high content of the saturated fatty acids and the very low proportion of unsaturated acids. Foreign substances interfere markedly with the germicidal activity of soap. It is suggested that linseed oil or cottonseed oil used in the manufacture of the official sapomollis might be advantageously replaced by coconut oil. The greater use of coconut oil soap would aid in the prevention of the spread of typhoid fever by hand contamination.

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ORIGINAL ARTICLES.

THE NATURE AND MODE OF REGULATION OF GLOMERULAR
FUNCTION.*

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THE literature of investigations of the function of the kidney reveals two distinct types of work. In one the kidney has been studied as one unit in the aggregate of organs which makes up the animal body—a unit upon the normality of whose function the welfare of the rest of the body depends. In such study the reactions of the kidney as a whole to changes in the conditions under which it works have been determined and expressed in terms of change in amount and character of urine eliminated. Such study has had the highest importance in the development of conceptions of the rôle which the kidney plays in the maintenance of that constancy of composition of body tissues and fluids which is essential for health; and it has directly aided the physician in practical problems in which he is required to detect and to evaluate abnormalities of renal function encountered in disease. For the purpose of such study it is not at all inconsistent with the requirements of scientific inquiry to regard the kidney itself as a unit, to speak figuratively, as a sieve with blood pouring into one opening and urine issuing from another—a sieve whose inlet, outlet and size of

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mesh are exquisitely adaptable to the necessities of the organism as a whole. Such expressions as "renal permeability," "renal threshold" are current illustrations of this implication.

In the second group of investigations are to be found those studies of kidney function in which effort is made to analyze the fashion in which the kidney performs its work. The basis of these efforts is recognition of the fact that the kidney, far from being a homogeneous structure, is a compact assemblage of millions of minute structures, and each of these, in turn, is composed of a number of highly differentiated parts; and that these minute parts are functionally adjusted with incredible nicety not only to each other but to the activities of the rest of the body as well. It is the aim of the student who wishes to analyze the function of the kidney on this basis to cultivate sufficient imagination and skill in experimentation to accomplish the identification and separate study of the functions of each different structure of which the kidney is composed, to the end that eventually he may obtain a conception of the workings of the kidney as a whole which includes an understanding of the contribution which each element of the kidney supplies. The results of such study are not apt to yield direct and immediate assistance to the physician in the solution of practical problems; but if they lead to sounder conceptions of the fundamental processes of kidney function they can hardly fail to furnish the basis for greater discernment and better judgment in practical tasks which concern it.

The work which I propose to describe belongs in this second category. It has been proceeding for ten years in the laboratory of which I am in charge and it is still in progress. The work would not have been possible except for the collaboration of a number of colleagues whose names I shall mention in appropriate connections and to whom the highest credit should be given.

The title of this account, "The Nature and Mode of Regulation of Glomerular Function," intimates the restriction of our discussion to one small part of the kidney. I think that we have enough information concerning glomerular function to warrant this; and I wished to make this choice of title implicitly express my conviction that until we can arrive at a reasonably accurate understanding of the part played by glomerular structures in urine formation, our footholds for progress toward elucidation of the function of the renal tubules are insecure. The literature of renal physiology contains an enormous amount of speculation, owing to the fact that intricacy of structure has made unambiguous experiment difficult. When we shall have designed and made unambiguous experiments on the glomerulus of such sort as to remove or lessen materially the necessity of speculation concerning its function we shall surely find that the speculative element in a consideration of tubular function is diminished.

Bowman,¹ in 1842, was the first who satisfactorily demonstrated that the tuft of capillaries which we call the glomerulus is actually inserted into the end of the tubule, the modified wall of which is expanded to form the capsule in which the tuft is enclosed. Hence the intracapsular space is the beginning of the lumen of the renal tubule. He advanced the view that fluid leaves the blood as it passes through the glomerular capillaries, and that this fluid, washing the inner surface of the cells composing the tubule, carries away the products of their secretory activity. He conceived the glomeruli to act as an automatic "sluice" by which water, salts of which the body was not in need, and many foreign substances were eliminated. Experimental evidence supporting the correctness of this view that fluid issues from the glomerular capillaries was supplied by Nussbaum² in 1878; indirect evidence was adduced by Brodie and Mackenzie³ in 1914. But in 1922 and 1923 W. N. F. Woodland⁴ published a series of studies of the frog's kidney which led him to the view that the glomerulus has nothing whatever to do with the actual production of urine but acts rather as a pressure-reducing valve in the circulation to the tubules, by which he conceives the entire urine to be secreted. It is not necessary to enter upon a detailed critique of Woodland's work. But since the question raised is fundamental to the discussion which I am beginning, it must of necessity be answered. The answer which, I think, completely controverts Woodland is found in an observation by Wearn⁵ made in our laboratory. By methods presently to be described, we taught ourselves to penetrate Bowman's capsule in the frog's kidney with a very finely pointed capillary pipette. By this means fluid from the capsule could be collected continuously for many hours. When blood ceased flowing through the glomerular capillaries fluid ceased rising in the capillary tube, though interruption of glomerular flow in the frog does not entail interruption in flow through vessels supplying tubules. In one experiment, by accident rather than by design, the opening from capsular space into the lumen of tubule was closed by a droplet of mercury injected into the capsular space. Accumulation of glomerular fluid in the pipette, previously slow and unsatisfactory, now became rapid. This observation demonstrates in conclusive fashion the correctness of Bowman's assumption and the fallacy of Woodland's.

Having proof that fluid which is eventually to become urine leaves the blood during its passage through the glomerular capillaries, we may take up the question of the nature of the responsible process involved. Examination of the arrangement of glomerular capillaries in contrast with capillaries in other areas shows certain definite differences. In the glomerulus a single arteriole, the vas afferens, breaks abruptly into a number of capillaries (in the frog three primary and six secondary branchings; in mammals, from the drawings of Bowman, many more). In the abrupt transition from

afferent vessel to glomerular capillaries the cross-section of the vascular bed increases many times; no such abrupt increase is found in other vascular areas. In the glomerulus the capillaries reassemble into the efferent vessel, smaller in diameter than the afferent; whereas in other vascular areas the efferent veins are larger than the arteries. Further, the length of the smaller arterioles leading to the glomerular system of capillaries is less than is length of the arterioles leading to the capillaries in other tissues, and as a result the head of pressure in blood reaching the glomerular capillaries must be higher than that in blood reaching other capillary areas.

Such considerations as these led Ludwig to the view that the blood pressure in the capillaries of the glomerular tuft is higher than in other regions; and that in consequence a protein-free filtrate is pressed out of the plasma through the capillary wall.⁶ This is the filtration theory. It received support from experiments in which a parallelism was shown to exist between urine formation and renal arterial blood pressure. After general acceptance for some thirty years it was effectively attacked by Heidenhain,⁷ on three chief grounds: (1) That certain dyes, injected into the circulation, appear to be eliminated by the tubules and not by the glomerulus, as judged by the appearance of sections of the kidney made after death; (2) that partial obstruction of the renal vein—a measure conceived to be capable of increasing pressure in the glomerular vessels—does not increase urine; (3) that the amount of glomerular filtration necessary to unload from the blood the amount of urea which is eliminated daily by the kidney was incredibly large when compared with his estimate of daily volume of blood flow through the renal vessels. These apparently insuperable objections led Heidenhain to substitute for the filtration theory an hypothesis which ascribed to the epithelium known to envelop the glomerular capillaries a power of causing the withdrawal of a fluid from the blood passing through these capillaries. Ludwig, in advancing the filtration theory, was obliged to attach to it a theory that reabsorption occurs in the tubules. Heidenhain, denying filtration, saw no need of a reabsorptive process, but saw in his results evidence of a secretory process in tubule cells. Following Heidenhain's work faith in the filtration hypothesis diminished. It was revived, however, some twenty-five years later by the work of Starling,⁸ in which was demonstrated the striking coincidence between the osmotic pressure of the plasma colloids and the values which he was able to assign for the minimal glomerular capillary pressure at which urine was formed. As late as 1910, however, opinions held by competent students of kidney function were divided on this question.⁹

The question is one which is of a great deal of interest to one who is obliged to interpret the diuretic action of drugs, for the

reason that the interpretation of such action can be no more convincing than is his conception of the processes which the drugs affect. The beginning of the experiments which we have made was undertaken for the purpose of discovering whether the secretory theory of renal function was better suited to explain the action of caffeine upon the kidney than was the filtration theory. An apparatus was made by Drinker and myself,¹⁰ by which blood could be passed through the living kidney of a rabbit *in situ* in a manner which closely resembled that in which blood is pumped by the animal's heart, but with one difference, that the mechanical pump which we arranged was constant in its output regardless of the state of dilatation or constriction of the vessels through which the blood was pumped. Plant and I applied the apparatus to the study of the action of caffeine on the rabbit's kidney *in situ*.¹¹ It was our thought that if caffeine were not capable of producing diuresis under conditions which did not permit alteration in blood flow through the kidney, the conclusion would be justified that the normal diuretic action of caffeine is a vascular one. The result showed, however, that caffeine was able to produce marked diuresis under the conditions stated, and for a time, therefore, we were inclined to regard our results as in harmony with the secretory theory of urinary production.*

But during these experiments it became obvious that we had in our hands a method for an attack upon the problem of the nature of the forces which are responsible for urine formation more direct than any previously available. We had found it possible to maintain the activity of the living kidney with an artificial and controllable circulation of blood through its vessels. It was easily possible to vary the pressure within this artificial circulation without at the same time necessarily influencing the volume of blood flow through the organ per minute. Hence it appeared possible to test the validity of the filtration hypothesis by keeping all recognizable conditions constant with one exception, viz: pressure of blood flowing through its vessels. The experiment was made many times with the uniform result that under conditions which completely prevented an increase in blood flow through the kidney, any considerable increase in pressure was associated with a parallel increase in urinary output.¹² The means by which pressure was raised in these experiments were stimulation of the splanchnic nerve, injection of adrenalin into the circulation and partial obstruction of the renal vein. None of those agencies commonly causes diuresis in the intact animal, because they all lessen the blood flow

* The explanation which we now assign to the diuretic effect of caffeine under these conditions is to be found in the experiments on pages 793, 795, 796. They provide reasons for believing that caffeine caused increase in glomerular capillary pressure and in number of glomerular capillaries through which blood was flowing; hence it increased glomerular filtration.

in the renal vessels. In our experiment blood flow was not diminished because of the efficiency of our pump, and the relationship between renal blood pressure and urine flow was clearly revealed.

For the first time indubitable evidence was gained that alterations in pressure alone in the renal circulation were responsible for alterations in urinary output, and the experiments may be regarded as the most direct evidence in support of the filtration hypothesis available at the time they were made. By a similar method Dreyer and Verney,¹³ in Starling's laboratory, have recently obtained similar results.

My reason for having introduced into this discussion an account of these old experiments is that their results, decisively confirmatory of the observations and reasoning of Ludwig's followers and decisively refuting one of Heidenhain's chief objections, gave us a conviction of the essential soundness of the filtration hypothesis which subsequent experience has not shaken; and they provided suggestions for the design of further experiments which otherwise would not have occurred to us.

In the experiments which immediately followed these, evidence was obtained bearing upon the regulation of glomerular function. These I shall presently describe. A further outcome has been the design of two series of experiments which bear, the one indirectly, the other directly, upon the nature of the glomerular process. This work was based upon the observation which had been made by Dr. Schmidt and myself, that it is possible to apply, after the manner of Krogh, methods of direct illumination to the kidney of the frog with the result that the glomerular vessels and the blood flowing through them becomes easily accessible to direct microscopic vision. Through the work of Barbour, Kite and, more recently, Chambers¹⁴ methods have been developed for microdissection and microinjections. Professor Chambers, of Cornell, has been able to make capillary pipettes of such extreme fineness that, using a mechanical manipulator of his design, it has been possible to inject foreign substances into the protoplasm of living cells. His demonstration in Philadelphia (1921) excited me to the belief that instruments of this type might become valuable as aids in the solution of a number of problems which concern the behavior of the renal vessels. Dr. Wearn, learning of this thought, transmuted it into the suggestion that by means of such a pipette it might be possible to enter the capsule of Bowman and withdraw the fluid as it collected there, with the hope of subjecting it to study.¹⁵ Our joint efforts resulted in the construction of a simple apparatus by means of which a slender pointed tube could be introduced into the intracapsular space and the glomerular fluid collected. Refinements of current methods of testing were introduced so that the minute quantities of fluid available could be subjected to accurate qualitative tests. The filtration theory of Ludwig's states

that as a result of pressure in the intraglomerular capillaries a protein-free filtrate from plasma passes through the walls of the glomerular capillaries into the space within Bowman's capsule. Our first task, after sufficient manipulative skill had been cultivated, was to test the fluid so obtained for protein. In some fifteen experiments the acetic acid-potassium ferrocyanid test was applied with negative results. Similarly tested a 1 to 100 dilution of frog's plasma gave unmistakable reaction. In other experiments the glomerular fluid was examined for chlorids and in still others for sugar. The urine of the frog kept in fresh running water contains only a faint trace of chlorid (as a rule not more than 0.05 per cent), and if the frog is kept for a day or two in distilled water the urine became completely chlorid-free as judged by the usual test. The glomerular fluid taken from Bowman's capsule of such a frog contains chlorid in impressive quantity.

The bladder urine of frogs, kept under ordinary conditions, contains no sugar detectable by Fehling's solution. The glomerular fluid, however, always reduces Fehling's solution when drawn from frogs whose blood contains detectable amounts of sugar. In our first experiments, made during the months of November and December, no reducing power could be detected in glomerular fluid, but when the blood of these frogs was examined by McLean's method sugar was found to be absent. On repeating the experiment during these months with frogs which had been injected subcutaneously with small amounts of glucose unmistakable reduction tests were obtained in the glomerular fluid. If sugar was injected in sufficient quantity to establish a blood-sugar concentration of 0.066 per cent or more, then sugar appeared in the bladder urine, but in such instances the degree of reduction by the glomerular fluid was decidedly greater than that by the bladder urine.

These experiments, then, revealed by direct tests the absence of protein and the presence of chlorid and of sugar in the fluid leaving the blood stream flowing through the glomerular capillaries, and are completely in accord, in so far as they go, with the demands of the filtration theory. They contain incontestable proof of the reality of reabsorption within the tubules, and provide the basis for further argumentative support of the view that the glomerular function is a physical rather than a "vital" or "secretory" one. Frogs, as we keep them in our tanks, get little or nothing to eat, and living in fresh water their supply of salts is extremely restricted. If they are to survive, they must retain their bodily store of salt and their nutrition is certainly largely dependent upon conservation of the carbohydrates in their tissues. The experiments show that the glomerular process is one which is not adapted to these conservations and that the escape of chlorid and of sugar which takes place there in these animals, disastrous if uncorrected, is actually corrected by the activity of the epithelium lining the

tubules. Such lack of adaptation to the needs of the organism is not commonly encountered in the case of processes which we designate as vital or secretory and may be regarded as indirect evidence that the glomerular process is a physical one.

Another aspect of this matter, however, has become evident as the result of a further series of experiments designed to secure information of the quantitative composition of glomerular fluid in comparison with blood plasma and bladder urine. At first it seemed hopeless to attempt to subject amounts of fluid ranging from 1 to 5 mg. in weight to the various manipulations which are involved in any quantitative procedure. The question, however, is so fundamentally important, from the standpoint of our conception of renal function, that it warranted extraordinary effort. Prof. Theodore Richards, of Cambridge, in his study of the atomic weights of sodium and chlorine, introduced the nephelometric method of estimating silver chlorid in extremely small amounts.¹⁶ We spent months in practice with his method as applied to minute amounts of known NaCl solutions, and at the end of a distressing period of probation were consistently able to estimate amounts of NaCl of the order of 0.01 mg. contained in 0.002 cc of water, with a degree of accuracy not far removed from that which obtains in ordinary quantitative work. The average error in the last six consecutive control estimations was 2.3 per cent.

We applied this method to the fluid taken from Bowman's capsule of frogs.¹⁷ In 3 experiments the figures for glomerular sodium chlorid were so nearly identical with those for plasma sodium chlorid from the same frogs (3 to 9 per cent higher), that one could well believe that the demands of the filtration theory as currently accepted were satisfied within experimental error. But in 7 experiments the discrepancy was too great to be accounted for by experimental error. In 5 of these glomerular Cl was higher than plasma Cl by 17 to 31 per cent of the latter; in 2 by 49 and 100 per cent respectively.

In another series of experiments a partially successful attempt was made to estimate urea in glomerular urine. The results are not so numerous and we do not regard them as so accurate as those of Cl. They indicated a decidedly greater concentration of urea in glomerular urine than in plasma.

We see an intimation in these results that the current conception of filtration as derived from filter paper or other inanimate material may require modification when it is transferred to the process of filtration as it may be going on through the walls of microscopic tubes consisting of living capillary endothelium covered by a tenuous layer of epithelium. It may be suggested that these figures indicate glomerular "secretion." I do not think that this is the case. They rather show the necessity of a further scrupulous investigation of the fashion in which a physical process may be

modified when it takes place through the living walls of tubes of capillary size.

The information which has already been presented may be summarized as follows:

Direct evidence has been described showing that fluid issues from the blood during its passage through the glomerular capillaries. Under favorable conditions the rate of issue may be disproportionately large in comparison with the rate of elimination of urine from the whole kidney. These facts correspond completely with Bowman's assumption and with the theory of Ludwig and disprove the recent contentions of Woodland.

Such fluid, collected under the most favorable experimental conditions, contains no protein—a fact which is directly opposed to the recent hypothesis of deHaan,¹⁸ whose work led him to conclude that colloids must normally be eliminated in the glomerulus and reabsorbed in the tubule. It contains both sugar and chlorid, while urine simultaneously collected from the whole kidney contains none. This shows a lack of adaptation of the glomerular process which requires correction, and this is accomplished by reabsorption of these substances during passage of the glomerular fluid through the tubules. This lack of adaptation is regarded as indirect evidence in support of the hypothesis that the glomerular function is physical rather than "secretory," filtration rather than secretion.

Under special conditions of experimentation it has been proved that urine elimination increases or decreases with increase or decrease in pressure in the renal bloodvessels, all other conditions so far as known remaining constant. On the assumption, warranted by anatomic considerations, that the effective site of action of pressure is the glomerulus, this fact affords strong support for the filtration theory.

Quantitative estimation of the chlorid content of the glomerular fluid in some instances is in harmony with the filtration theory; but exceptions to this statement have been encountered which indicates the necessity for a study of the fashion in which capillary forces and vitality of the glomerular membranes may influence the filtration process.

In a discussion of the mode of regulation of glomerular function it is vital to keep in mind the fact that the tuft of glomerular capillaries is interpolated between two vessels having the characteristics of arterioles. The afferent vessel is commonly described as having a diameter greater by one-half than that of the efferent vessel. Both are supplied with nerves which terminate upon the muscle cells contained in the wall. Whether nerves penetrate the capsule and make connection with the glomerular capillaries may be regarded as uncertain, though a statement to this effect is contained in the writings of the anatomist Smirnow.¹⁹

In the experiment which I have previously described in which the rabbit's kidney was perfused with blood at a constant rate and in which increase of pressure was found to be associated with increase in urinary output, the opportunity presented itself for a closer examination of the vascular reactions involved.²⁰ The experiment was repeated with the rabbit kidney, excised from the body and placed in an apparatus (oncometer) designed for recording changes in its size. After perfusion had begun, small amounts of adrenalin were added to the blood, entering the renal artery. Constriction of bloodvessels occurred, as was shown by prompt and decisive rise in perfusion pressure; but at the same time the size of the kidney increased. The conditions of the experiment were such that this increase could have been due only to dilatation of vessels within the kidney. Thus we were confronted with the paradoxical coincidence of vascular constriction and vascular dilatation in the same organ. Similar experiments were made with other organs of the body—legs and intestine—and in these the increase in pressure caused by adrenalin was invariably associated with diminution in size of the organ perfused. If now it is recalled that the renal circulation differs from that in other structures in that the distensible glomerular tufts are inserted between two contractile vessels, an explanation of this paradox suggests itself. The conditions of the experiments were such that constriction of the afferent vessel could have little or no effect upon the volume of blood entering the vessels of the glomeruli; but constriction of the efferent vessels would inevitably cause increase in pressure in the capillaries proximal to it, despite the fact that no decrease in total amount of blood flowing through the kidney could have occurred. Here for the first time, in so far as my knowledge goes, was encountered experimental evidence of the contractility of vessels on the distal side of the glomerular tuft and the suggestion was obvious that we were dealing with a mechanism which is normally concerned in the regulation of intraglomerular pressure, and therefore of glomerular function.

The suggestion had been specifically made by others²¹ that glomerular pressure may be subject to regulation by the relative diameters of the afferent and efferent vessels, but up to this time the question had not become accessible to experimental approach.

In order to relieve our experiments of the stigma which is commonly attached to perfusion experiments in which reduction of variables is secured at the expense of normality of conditions, we planned a series of experiments based upon this thought: The efferent vessel is by common consent smaller than the afferent vessel; an equal degree of vasoconstriction involving the two vessels alike could be expected to produce a greater increase in frictional resistance in the smaller vessel than in the greater. Hence if one could select a dosage of a substance whose action included

constriction of renal arterioles of exactly the suitable degree of magnitude, he might expect to demonstrate a greater degree of obstruction in the efferent vessel than in the afferent, and the expected manifestations of such action would be a coincidence of slight increase in general aortic pressure, diminution in volume of blood flowing through the kidney, increase in size of the kidney and increase in urinary output. After many trials a few experiments have been successfully carried through in which we think the technical demands of the problem were successfully met, and the results completely correspond with the hypothesis on which the experiment was based.²² In eviscerated rabbits minute dosage with adrenalin, with pituitary extract and with barium chlorid, gave rise to the coincident events upon which I have laid emphasis.

While we were unable to imagine another explanation equally acceptable, an intense desire was aroused for finding another method of test of the hypothesis. It was this desire which led me to think that it might be possible to subject the frog's kidney to methods which permit direct microscopic observation. If such method should prove successful we might obtain direct visual evidence that constrictor substances acting in high dilution produce a greater degree of constriction of the efferent than of the afferent vessel. I invited Dr. Schmidt to collaborate with me in the effort to apply the methods which were at that time being developed by Professor Krogh in other connections, and we soon discovered that it was a relatively simple matter to subject the glomerular circulation of the frog to direct inspection.²³ So far as I know, this had not been previously successfully accomplished. Our first experiments were designed to discover whether the intravenous injection of minute amounts of adrenalin were capable of causing an enlargement of the glomerular tuft in a manner compatible with the conditions which I have presented. The results in the main were favorable to our conception. In many experiments the introduction of 0.001 mg. of adrenalin caused flow of blood through the glomerular channels to be retarded, and caused measurable increase in the diameter of the capillary tuft. This was regarded as evidence that the efferent vessel contracted. We could not subject the efferent and the afferent vessels to direct measurement, because as a rule their outlines were obscured by overlying tissue.

While this result was in harmony with those of the mammalian experiments, we conceived one source of possible error as attached to it. Adrenalin not only affects the vessels of the frog's kidney but also those of other tissues; it also increases the activity of the heart. The effect, therefore, which we observed might conceivably be the result of increased blood supply to the kidney consequent upon cardiac stimulation and increased aortic pressure. It was therefore incumbent to design a perfusion experiment with the frog's kidney similar to that which had been made with the rabbit,

so that the blood flow through the frog's kidney should be constant regardless of the state of dilatation or constriction of the renal vessels. That there are technical difficulties to be encountered in such an experiment is obvious and a successful attempt to overcome this has only recently been made in collaboration with Mr. Bradley and Dr. Barnwell: Two syringes of identical caliber were filled with the whole blood from other frogs and arranged so that the contents of either could be driven at constant rate through the vessels of the kidney *via* the renal arteries. Adrenalin to make a concentration of 1 to 500,000 was added to the blood in one syringe. The animal was adjusted on the stage of a microscope provided with a photomicrographic camera so that photographs of glomerular tufts could be taken at frequent intervals during the course of the experiment. Substitution of blood containing this minute amount of added adrenalin for blood containing none caused an unmistakable increase in the size of the glomerular tufts which were under observation. Simultaneous records of pressure in the renal artery and of the amount of blood issuing from the renal vein showed the characteristic constriction of renal vessels but without any diminution in the rate of passage of blood through the entire organ. The objections which had been made to the acceptance of our conclusions from the experiment on the intact frog seem, therefore, to have been overcome, and we regard this as strong evidence that an increase in intraglomerular pressure may result from constriction of the efferent vessel.

In these experiments attention has been concentrated upon effects which may be produced by minute amounts of the substance adrenalin. We were not primarily interested in the action of this substance as a drug; its great interest for us lies in the fact that it is a hormone which normally circulates in the blood and takes part, we believe, in circulatory adjustments of the most exquisite kind. Its action on bloodvessels, as is well known, is identical with that of sympathetic nerve stimulation, and hence in exposing the intricacies of its action we gain information which is applicable also to nervous control of the renal vessels.

These experiments provide the basis for thinking that very small amounts of adrenalin or very slight stimulation of sympathetic nerves to the kidney may increase intraglomerular pressure by more effective action on efferent than on afferent vessels; while larger amounts of adrenalin or more intense nerve stimulation, by causing constriction of both, lessen both glomerular pressure and glomerular blood flow. The former influence would result in diuresis; the latter in diminished urine; and it is known that each of these effects may be elicited by adrenalin if dosage be suitably chosen. It seems to me wholly probable that both types of action may be exerted by concentrations of adrenalin which exist at

different times in the arterial blood as the result of activity of the suprarenal glands.

Another aspect of the same problem concerns the action of dilator substances. It has long been known that substances which pass readily into the urine and which cause diuresis cause also dilatation of the renal bloodvessels. I refer to increased water content of the blood, to such salts as sodium chlorid, sodium sulphate, sodium bicarbonate, and to sugar, to urea, to caffein and its derivatives. It is at once obvious that any substance which dilates renal bloodvessels without simultaneously producing a fall in aortic pressure will thereby increase the rate of blood flow through the kidney. Such increased blood flow *per se* would be a diuretic factor, for the reason that the rate of renewal of contact of fluid from which filtrate is produced with the membranes through which the filtrate passes would be increased. But whether or not intraglomerular pressure will be increased by vascular dilatation of the kidney will depend upon the relative degree of action upon afferent vessels and upon efferent vessels or vessels distal to the glomerular tuft. The question is therefore pertinent whether such substances as I have mentioned possess the power of dilating the afferent vessels to a greater degree than the efferent vessels.

There were some *a priori* reasons for imagining that this might be the case. We have proved that between the afferent and the efferent arteriole the blood plasma is concentrated by loss of fluid which contains no protein. Consequently the colloid content of the plasma of the blood which is flowing through the efferent vessel is greater than that of the plasma of blood flowing through the afferent vessel; the question therefore arose whether the colloid concentration of fluid in which a vasodilator substance is dissolved may affect the intensity of its action. This suggestion, made four years ago,²⁴ has only recently been subjected to experimental test. Hamburger's modification of Ringer's solution was adopted as a suitable fluid with which to perfuse the vessels of the frog's kidney from a glass reservoir in the usual way. Four solutions were prepared for a single experiment, two containing as a colloid purified acacia in concentration of 3 per cent. Two other solutions were similarly prepared in which the colloid concentration was 6 per cent. Caffein in amount to make 0.1 per cent was added to one sample of the 3 per cent acacia, and to one sample of the 6 per cent acacia. The arrangement of perfusion reservoirs was such as to permit accurate comparison of the dilating action of 0.1 per cent caffein in 3 per cent acacia with that of 0.1 per cent caffein in 6 per cent acacia. Results were expressed in terms of rate of flow through the organ per minute, perfusion pressure being maintained constant. The result exceeded expectations. In every instance it was found that the dilator action of caffein in 6 per cent acacia is very markedly less than in 3 per cent acacia. Similar

results were obtained in experiments in which sodium nitrite and sodium chlorid were tested.

These results show that the peculiar arrangement of the glomerular capillaries in relation to the afferent and efferent arterioles is such that substances which dilate these arterioles produce greater dilatation of the afferent than of the efferent. Thus intraglomerular pressure is raised and increased filtration occurs. Since we know that renal vessels react very sensitively to dilator substances, we can see how it is that a slight increase in water, salt, urea content, etc., of the blood automatically produces such an alteration of these vessels as to provide conditions favorable for increased glomerular elimination and hence for ridding the blood of such excess.

While our first observations on the effect of minute doses of adrenalin on the size of the glomerular tuft were in progress, other features of the glomerular circulation became apparent, and it was soon evident that these might properly be looked upon as evidences of the fashion in which glomerular function is adjusted to bodily requirements.²⁵ Some preparations of the frog's kidney were encountered in which very few glomeruli were visible; in others many were to be seen. The visibility of the glomeruli was dependent upon the presence of blood corpuscles within their capillaries. We soon found that the number of visible glomeruli in a preparation in which it was small could be increased by many of the common means of increasing renal circulation, such as section of the sympathetic nerve supply, injection of salt solution, transfusion of blood, injection of salts, of sugar, of urea, etc. On the other hand, the number could be diminished by means which are known to produce constriction of renal vessels, such as stimulation of sympathetic, large doses of adrenalin, or of pituitary extract. These observations yielded proof that in the frog's kidney the fraction of the total glomerular equipment which receives blood and hence which functions at any one time is variable, and thus evidence is afforded in support of the conception that the degree of glomerular activity of the whole kidney is susceptible of adjustment by increase or decrease in the number of glomerular units which are active. This conception was very clearly stated sixty-five years ago by Hermann,²⁶ a colleague of Ludwig's, but, so far as I know, no definite experimental evidence in support of it has previously been advanced. It is well known that comparatively slight changes in the composition of the blood—changes which are hardly discoverable by chemical means—are capable of producing a diuretic response which seems disproportionately great. If we conceive that a renal vasodilator substance increases the rapidity of renewal of blood plasma in contact with glomerular surface, increases intraglomerular pressure by a greater degree of dilating action upon the afferent than upon the efferent vessel, and in addition causes an

actual increase in the number of glomerular units involved, we have the basis of an explanation of such apparent disproportionate effects. It will be recalled that the work of Gotch, Keith Lucas, Lodholz, and Adrian²⁷ showed that the intensity of response by muscle to stimulation of its motor nerve is dependent upon the number of fibers in the nerve which take part in the transmission of the impulse. It will be recalled that Krogh showed that the number of patent capillaries in a muscle varies with the physiologic state of the muscle.²⁸ Our observations show that the number of glomerular units which take part in renal activity may similarly vary to meet changing demand on the part of the organism for excretory function.

These observations on the frog's kidney will not be accepted as immediately transferable to the physiology of the mammalian or human kidney without question. Thus far it has not been possible successfully to subject the mammalian kidney to methods of direct observation. But in respect of variability of number of glomeruli involved in the function of the whole kidney at any one moment, indirect methods are available. Kanolkhar,²⁹ in London, injected hemoglobin solutions intravenously into animals, removed the kidney and in thick sections of the cortex counted the number of glomeruli which showed traces of hemoglobin and of those which did not, he came to the conclusion that events similar to those which we had described in the frog's kidney took place in the mammalian kidney. Dr. Hayman and Dr. Starr,³⁰ in our laboratory, have carried through a series of experiments similar to these in design. They used Nelson's method for estimating the number of glomeruli.³¹ This consists in staining the glomerular tufts by passing a solution of Janus Green B through the renal vessels, dissecting the cortex away from the medulla, and counting the stained tufts in a small weighed section of the cortex. Knowing the weight of the whole cortex, the total glomerular count for the whole kidney is easily ascertainable. After convincing themselves of the reliability of the method, they found that the number of glomeruli in the two kidneys in a normal rabbit is approximately the same. Then the following procedure was adopted. From the anesthetized rabbit suitably prepared, one kidney was excised without hemorrhage, and laid aside for subsequent enumeration of the total number of glomeruli in it. The condition to be studied was then established in the animal, (that is, injection of diuretic, of adrenalin, and so forth) a solution of Janus Green B injected into the aorta above the remaining kidney, and within twenty seconds of the end of the injection this kidney was excised. Obviously the dye could reach only such glomeruli as were receiving blood at the time of injection and during succeeding seconds. Glomerular count of the intravitaly stained kidney compared with the total glomerular count of the other showed the fraction of glomeruli which were

receiving blood during the presence of the dye in the circulation. A long series of experiments was made, the results of which are convincing. They showed that from 50 to 85 per cent of the total glomerular equipment of the rabbit receive blood under control conditions. If a diuretic, such as caffein or NaCl, was given from 95 to 100 per cent of glomeruli receive blood. If graded doses of adrenalin were given, or if vasoconstriction were produced by inhalation of CO₂, or if the splanchnic nerve were stimulated, the number of glomeruli receiving blood could be diminished at will to 40, 30, 20, 10 or 5 per cent of the total glomeruli present. These experiments appear to me to furnish adequate proof that the observations made on the frog are acceptable for the interpretation of events which take place in the mammalian organ.

Proceeding from the conception that mechanisms are at the disposal of the kidney, whereby a greater or smaller number of its glomerular units may be utilized in the filtration of fluid from the blood in accordance with the excretory requirements of the body, we may properly ask how it is that damage is avoided to those glomerular structures through which temporarily no blood is flowing? One of the oldest observations in the history of renal physiology is to the effect that interruption of the renal circulation for a short time (minutes) results in albuminuria when the interruption has ceased. If, then, during any prolonged period the kidney uses, let us say, only 60 per cent of its glomeruli, how is it that the other 40 per cent escapes the damage which could be expected to result from lack of circulation through them? The answer to this question begins in observations which were made immediately after we had discovered how to look at the glomerular circulation in the frog's kidney. It was seen that the flow of blood through the glomerular capillaries in many experiments was not continuous, but was irregularly intermittent. This intermittence was not synchronous with the heart beats, nor was it uniform or regular for individual glomeruli which could be simultaneously observed. This observation suggested the probability that while the total number of glomeruli of the kidney were not necessarily suffused with blood at any one moment, yet by individual variations of blood flow in individual glomeruli the total glomerular equipment might be suffused within a period short enough to prevent the damage which more prolonged anemia would entail; and this suggestion was adopted as an interpretation of the broader significance of the observed interruptions in glomerular flow.

But how this phenomenon of intermittence is produced was for a long time a complete mystery. It became clear that the intermittent cessations of blood flow through individual glomerular tufts were not due to constrictions of capillaries composing the tufts. It could be seen that intermittent flow included the arterioles leading to the tuft, and hence the glomerular cessations are in

reality arterial or arteriolar phenomena. Finally Langley's work³² on the nervous control of the smaller arteries in the web of the frog's foot was encountered, and its bearing upon our problem recognized. He showed that when a nerve supplying a vascular area in the frog's web is stimulated repeatedly the resultant constrictions of the smaller arteries do not uniformly involve the same vessels; vessels which contract to one stimulus are not necessarily the same as those which responded to the preceding one. He made the suggestion that the physiologic condition of the muscle of the arteriole may so vary as a result of its contraction that at one time it may be refractory to a stimulus to which it responds at another. This led me to think that in the kidney the smallest arterioles might undergo alterations in their readiness to respond to constrictor influences and that such alterations might be responsible for the observed intermittence. In harmony with this thought was the observation that intermittence is most apt to be encountered in the frog if the upper part of the spinal cord has not been injured in the process of destroying the brain, the operation which we use to avoid the necessity of anesthesia. The upper part of the spinal cord in frogs contains a large share of the central nervous mechanism for controlling the caliber of the bloodvessels. It appeared, then, that it might be possible to produce artificially an intermittence of the glomerular circulation by subjecting the vessels of the kidney to a constant constrictor influence of a moderate grade of intensity. Three groups of experiments were made. In one the central end of the sciatic nerve was stimulated during observation of blood flow through a group of glomeruli; in another the ramus communicans from the fifth spinal nerve which contains vasoconstrictor fibers to the kidney was stimulated; and in the third a dilute solution of adrenalin was injected at an extremely slow but constant rate into the abdominal vein. In each experiment a group of glomeruli was closely watched before, during and after the period of stimulation. It became very clear that each of these three means was capable of inaugurating in a previously uniform glomerular circulation an intermittence precisely similar to that which we had previously seen occur spontaneously. And hence we have the basis for belief that when the bloodvessels of the kidney are subjected to a constant nervous or chemical constrictor stimulus the response exhibited by the vessels concerned is an intermittent one. We picture the process to occur as follows: It has been known since the time of Lister and Cohnheim that if a vascular area is rendered anemic by clamping its artery for a time, when blood is readmitted, the vessels are dilated as though their tonus had been diminished by the asphyxia to which they had been subjected. Some years ago I found that when the vessels of the heart or the vessels of the leg of a dog were perfused with fully oxygenated Ringer's solution the substitution of identical Ringer's solution containing no oxygen

caused them to dilate immediately.³³ We may therefore regard it as proved that lack of oxygen has a dilator influence upon arterial muscle. If, then, a small artery in the kidney is constricted as a result of a nervous or chemical influence so that no blood passes through it, the asphyxia of its muscle so induced leads to a progressive decrease in its power to continue reacting to that stimulus; so that eventually, assuming the stimulus to be moderate in degree, the muscle must relax, the artery opens and blood flow through it is resumed. When blood flow returns, and with it adequate nutrition of the muscle wall of the arteriole, this again becomes responsive to the constrictor stimulus and again the vessel may close. We may conceive such a process, involving many vessels, and hence many glomeruli, as capable of producing just such an intermittence as I have attempted to describe.

There is another fashion in which the surface of glomerular capillaries available for filtration is variable. The capillary pathway in the single tuft in the frog's kidney very often can be seen to consist of three primary branchings from the afferent vessel, each of which in turn undergoes a secondary branching. One frequently sees that the blood current entering a glomerulus flows largely into one of the three primary divisions and scantily into the other two. In some instances only one capillary channel will be seen in a tuft, but if any one of the various vasodilator influences which I have mentioned are introduced into the blood stream other capillary channels in this tuft may open and become visible by reason of the stream of corpuscles passing through. I have spoken of intermittence of the glomerular circulation, using this term to indicate the fact that blood often ceases to flow temporarily throughout the whole tuft; intermittences of individual capillaries within a single tuft have been plainly seen. In the most striking illustration of this fact which I have encountered the blood current through a tuft during the early minutes of observation was confined to one apparently dilated capillary. While I was watching the flow of blood through this a second capillary suddenly made its appearance, branching from the origin of the first; presently a third similarly appeared, and during the succeeding minutes of observation these two alternately opened and closed, while blood flow through the first remained steady and uninterrupted. When viewed by reflected light under varying circulatory conditions, remembering that the capillary pathway is discernible almost only by corpuscles passing through, the appearance of a single tuft may be so different at different times as to make it difficult to believe that it is a single structure which is under observation.

For a long time we were under the impression that these changes in capillaries within a single tuft were caused by changes in the caliber of the capillary presumably brought about as a result of nervous influence exerted upon it. One citation from the anatomic

literature can be advanced (Smirnow) indicating that nerve fibrils pass into the capsule of Bowman and are related to the capillaries enclosed within it; but when the changes which occur in the circulation within a single capillary of a glomerulus are more closely observed, using higher powers of the microscope, one fails to discover signs that the caliber of the capillary tube decreased during such interruptions as I have described. Into such a capillary a single corpuscle may be seen to enter. It passes slowly through and disappears, but during its passage it is not distorted as would necessarily be the case were the capillary narrowed, but on the contrary can be seen to rotate on its various axes and apparently to bump from side to side as though floating in transparent fluid flowing through a relatively wide tube. Observations of this sort have led to the view that alterations in the caliber of glomerular capillaries resulting from their own contractility are yet to be proved. Such events as those just described can be more satisfactorily accounted for by alterations in diameter of the openings from the afferent vessel into glomerular capillaries. We have suggested that these openings may have sphincter-like properties, may undergo rhythmic alterations in tonus and may be more sensitive to constrictor or dilator influence, nervous or otherwise, than is the capillary wall. Indeed, Dr. Schmidt made observations, and I have confirmed them,³⁴ which indicate that constrictions under the influence of adrenalin occur more effectively at branchings of the smaller arterioles in muscle than at intermediate points, and in the older literature are to be found descriptions of phenomena which accord well with this statement. In the very recent work of Landis on pressure within capillaries further evidence has been encountered which is in harmony with this statement.

Another mode of adjustment of glomerular filtration may be mentioned. It is obvious that the glomerular capillaries are in a peculiar situation in that they are enclosed by Bowman's capsule which forms a strong and highly elastic envelope. We know that fluid issues from these capillaries into the intracapsular space from which it flows into the tubule. We know that fluid in different capsules is subject to different degrees of pressure which depend upon the pressure within the glomerular capillaries, upon ease of passage of fluid through the walls of these, and upon ease of exit of fluid down the tubule. Evidence of such varying intracapsular pressures can be obtained by simple inspection of a kidney which is forming urine. The degree of distention of different capsules which come within the range of one's vision is highly different, and if uniform pressure is exerted upon the surface of a kidney by means of a fragment of coverslip, it is seen that the flow of blood may stop completely in the capillaries of one tuft, while it is vigorously maintained in those of another. Regarding the glomerular process as one of filtration, it is obvious that filtration pressure is the differ-

ence between the pressure inside the capillaries and the pressure outside. The more rapid the accumulation of the outside pressure, and the higher the point which it attains, the more rapidly must an impediment to filtration accumulate. Such an accumulating impediment must act as an automatic brake to the process. If one perfuses the frog's kidney with oxygenated salt solution to which a trace of India ink has been added to render the capillary tufts more easily visible, and if the pressure under which the perfusion fluid is flowing through the kidney is suddenly raised, many visible tufts undergo obvious increase in size. Some do not, but if after previous laceration of a few of the capsules of the visible glomeruli a similar increase in pressure is induced, then it is found that the increase in size of the capillary tuft in these is decidedly greater than before. In other words, the capsule of Bowman, which serves as a chamber for collecting the glomerular filtrate and transmitting it to the tubule, is also a protection to the glomerular capillaries enclosed in it, and prevents damage to these capillaries which might result from excessive capillary pressure; by the tension which it is capable of exerting over the fluid which is in it, it can slow down the filtration process. We are as yet ignorant of the pressures which exist in the glomerular capillaries and within the capsular space. The subject is one upon which Dr. Hayman is at present engaged, and the prospect is that we shall shortly have quantitative data by which to measure the correctness of these statements.

In review of the information which I have been able to present which bears on the question of glomerular regulation, it may be said that evidence now exists upon which to base belief that glomerular pressure and hence glomerular filtration is regulated not only by the gross circulatory events which have long been recognized, such as alterations in the arterial pressure, in the venous pressure and in the gross change of the renal vessels in relation to these, but also by fine adjustments of the caliber of the afferent and of the efferent vessel in relation to each other. The mode of adjustment is such as automatically to provide conditions suited to rid the blood of excess of any substances which dilate the renal arterioles and which pass through the glomerular membranes. The more important normal urinary constituents very certainly possess these properties. Evidence has been presented in support of the belief that the action of adrenalin includes constriction of the efferent vessel as well as of the afferent. The proved identity of the vascular actions of adrenalin with the effects of sympathetic nerve stimulation permits the results obtained with adrenalin to be applied to problems of nervous control of these vessels. The suggestion may be made that the normal state of tone of these minute arterioles, sustained by the tonic action of the sympathetic nerves and of circulating adrenalin is such as to maintain intraglomerular pres-

sure by slightly greater constriction of efferent vessel than of afferent, whereas an increased degree of vasoconstriction must diminish intraglomerular pressure by closing of the afferent vessel.

Glomerular regulation is also secured by changes in the number of glomerular tufts and of capillaries in the same tuft through which blood flows at any one time. This is equivalent to saying that the extent of endothelial surface available for filtration is variable, being increased by influences which dilate vessels and decreased by influences which constrict. Damage to the kidney by prolonged anemia of any of its parts is avoided by the provision of intermittence and this in turn is, we think, dependent upon the action of constrictor influences and the antagonistic dilator action of anemia which results from these.

Extracapillary intracapsular pressure which develops because of the elasticity of the capsule of Bowman, may act as an automatic brake upon the filtration process and at the same time is capable of protecting glomerular capillaries against undue distention from excessive intracapillary pressure.

We have described the process of filtration in the glomerulus as one not adapted to the interests of the organism as a whole, because it indiscriminately eliminates from the blood substances which the body should retain as well as those of which it should be rid. The tubule supplies the correction to this lack. But in the arrangements which have been developed for the circulatory control of the glomerular process we must see evidence of a very high degree of adaptation to the bodily welfare.

I have not touched upon the problem of permeability of glomerular membranes. I am convinced that variations in it occur and will eventually be demonstrated; but the direct experiment which compels belief has not been made.

Before closing, I wish to mention very briefly a series of experiments which may serve to relate some of the observations I have been describing to the practical problem of albuminuria. Four years ago it was suggested that if the period of intermittence of glomerular blood flow should be slightly lengthened an albuminuria might be anticipated to result.³⁵ The anticipation was based on the knowledge that temporary closure of the renal artery is followed by albuminuria and upon the evidence provided by Nussbaum that this is glomerular in origin.³⁶ Experiments were designed to test this thought and Dr. Starr has carried them out.³⁷ Normal healthy rabbits, given an intravenous injection of adrenalin in such amount and fashion that its action is maintained for several minutes, subsequently show transient albuminuria. Healthy cats, subjected to insults which they resent and which excite them to fear or rage, subsequently eliminate albumin. When the question was studied in anesthetized dogs under controllable conditions it was found that the course and degree of albuminuria which could

be produced by vasoconstrictor influences, such as adrenalin, stimulation of the splanchnic nerve, inhalation of CO_2 , and so forth, was strictly analogous to that which could be produced by temporary partial obstruction of the renal artery. In exceptional experiments no renal vasoconstriction was produced by these means, and in these albuminuria did not occur; thus showing that the albuminuria was dependent upon the vasoconstriction and was not the result of direct action of the agents tried upon the glomerular membranes. Histological study showed no abnormalities of structure in these kidneys. Similar results have been obtained in man in a study by Dr. Grier Miller, now in progress in the University Hospital, of the effects of ephedrin—a drug of Chinese origin recently studied by Dr. Schmidt and K. K. Chen, in Peking, samples of which have been supplied to us by Dr. Chen. Their work showed that ephedrin causes vasoconstriction similar to but more lasting than that of adrenalin. In the cases studied by Dr. Miller tests made by Dr. Starr for albumin in the urine were positive in those cases in which distinct rise in blood pressure occurred; negative in those in which it did not. Maximum albumin elimination did not coincide with maximum height of blood pressure, but followed it.

These results show how renal vasoconstriction can lead to albuminuria and how a diuretic which opens up glomerular vessels which have previously been closed may appear to be a damaging agent upon renal structures, whereas in reality the damage of which the eliminated albumin is evidence was the result of the vasoconstriction which the diuretic abolished.

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STUDIES IN HUMAN CONSTITUTION.

III. PHYSICAL TYPES IN RELATION TO THE TOXEMIAS OF PREGNANCY.

BY GEORGE DRAPER, M.D.

NEW YORK.

FOR some time past at the Sloane Maternity Hospital, there has been a growing belief that the women who developed idiopathic hypertension during the course of pregnancy were of a morphological type which could be recognized. Less marked, but still recognizable, characteristics could be noted in toxemic cases in which nephritis was the outstanding feature. At the request of Drs. Studdiford and Herrick,¹ the Constitution Clinic of the Presbyterian Hospital undertook to make anthropometric studies of a series of cases which they selected. No attempt was made to reclassify the toxemias of pregnancy, and no existing classification was used rigidly as a basis for their selection of cases.

As is well known, a variety of conditions have been described under the head of the toxemias of pregnancy. There are numerous classifications, such as those of Kosmak,² Schiotz,³ Cheney,⁴ Kellogg⁵ and others. These writers recognize besides the acute pernicious vomiting type and the acute yellow atrophy of the liver, in general two or three less fulminating forms in which high blood pressure or more or less severe nephritis appear either as the dominant symptom or in various combinations. The cases selected by Dr. Studdiford and Dr. Herrick included, so far as possible, examples either of idiopathic hypertension or nephritis. There were, of course, several individuals in whom both conditions existed. But when this was true the patient was classified according to the preponderance of one or the other. Because of the fact that the white race alone had figured in our previous studies, it seemed best at first to exclude negroes from the investigation. But the black race formed so

large a part of the total available material that it was finally decided to make comparative studies on these people also. Actually this turned out to be a most fortunate decision, for, as will be shown later, it provided a check on the method which had neither been sought nor expected.

The technic of measurement and the method of presenting the data in this study are essentially similar to those described in the author's book on *Human Constitution*. The material consisted of 117 cases, distributed as follows between the two races and the two pathological conditions:

White, hypertension	42 cases
White, nephritis	22 cases
Black, hypertension	25 cases
Black, nephritis	10 cases

It had been the impression at Sloane that the women with idiopathic hypertension were large, rather heavy-faced individuals, who often displayed hair distributions which suggested virilism. Indeed, with a proper academic restraint, they had been referred to as "pituitary types." Those patients whose predominant ailment was nephritis were not so well defined in character, but seemed to be in general smaller, thinner and less well developed.

For the satisfaction of the more critical students of this problem, it would be desirable to publish all the original numerical data gathered in the course of this investigation. But to present all the figures and tables in an article of this scope is impossible. They will be made available later however, in a larger monograph on the subject of hypertension and nephritis. For the present four figures are presented which show first of all, certain classical racial differences between the whites and blacks, and second, certain differences in bony structure between the two disease groups. The curves make apparent an interweaving of racial and disease group characters. From a technical standpoint these results are interesting and important because the same technic which correctly demonstrates the well-known anthropometric differences between the white and black races is applied to and shows equally great differences between the two disease groups.

In Fig. 1 appear in the form of cumulative percentage curves (Galton) differences in the radius length. Without entering upon an elaborate discussion of the structure of these curves, it may be said that displacements of the curves toward the right indicate greater lengths of radius. It will be seen that the difference between the races in respect of radius length is clearly shown by the grouping of the solid and broken line curves. Furthermore, it is apparent that the cross-hatched curve representing hypertension is in each instance on the long side of the uncross-hatched curve. These relationships reflect not only the accepted fact that the negro radius is longer than that of the white race, but also that in both

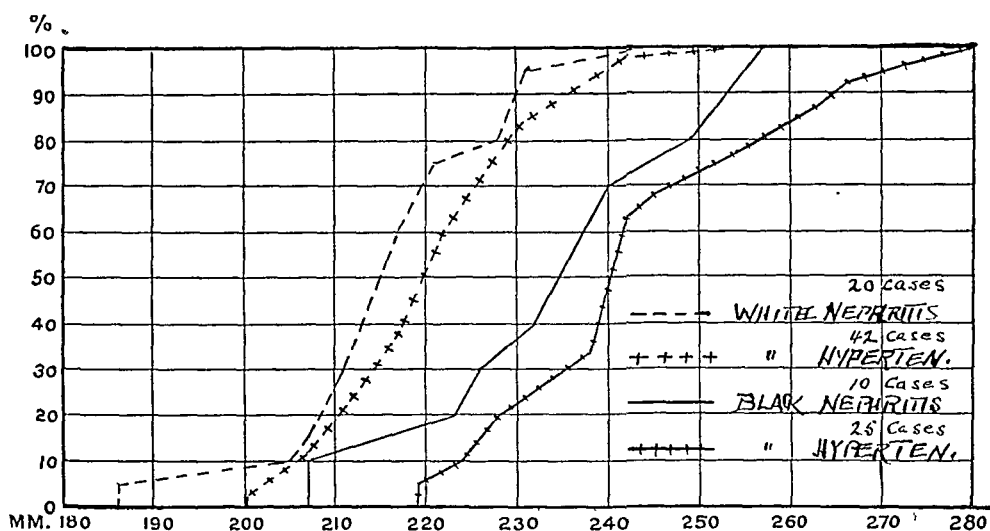


FIG. 1.—Radius length.

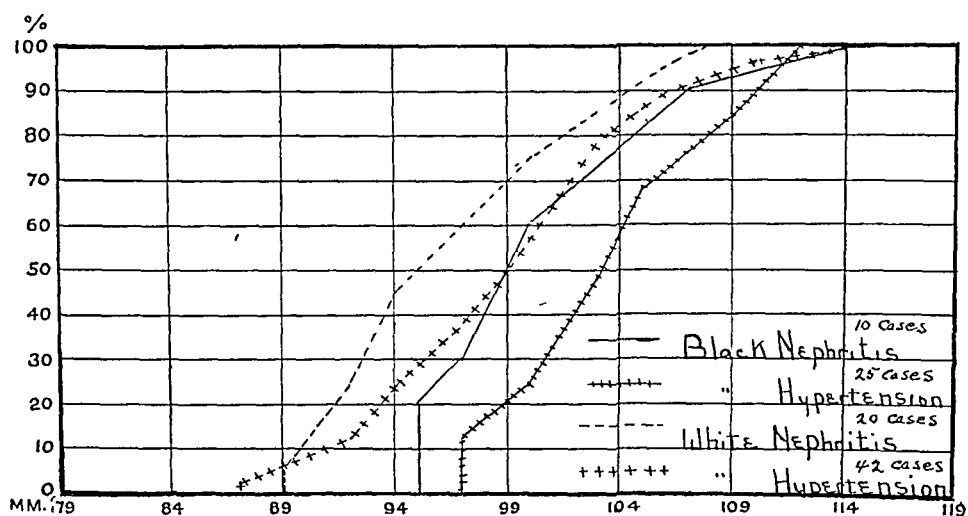


FIG. 2.—Palm length.

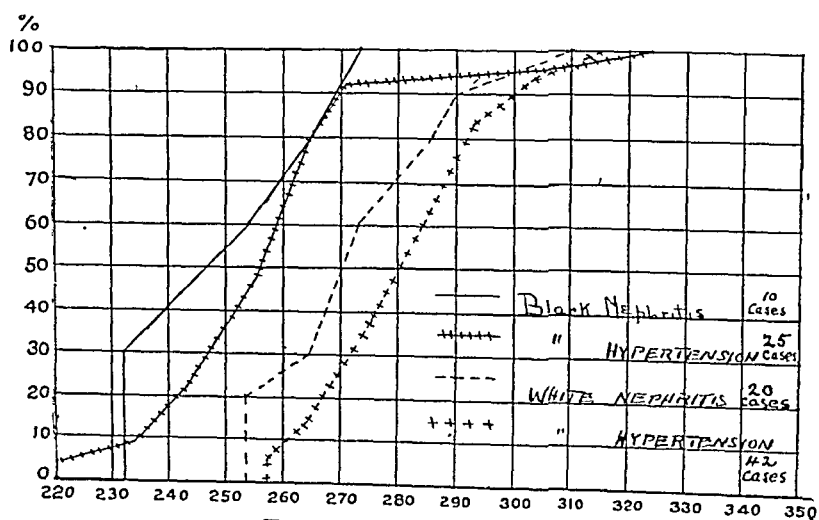


FIG. 3.—Bi-iliac diameter.

paces the radius length of women with hypertension form of pregnancy toxemia is greater than that of women suffering from nephritis. Similar relationships are shown in Figs. 2 and 3. The palm length, whose largest component is the metacarpal bones, is seen to be somewhat longer in the negro than the white race. But the greater length of the palm of the hypertension cases is likewise apparent. Fig. 3 illustrates still another well-recognized racial difference; namely, the narrower pelvis width of the blacks. In this measurement also the larger bony structure of the hypertension group declares itself. The curves in Fig. 4, which express chest

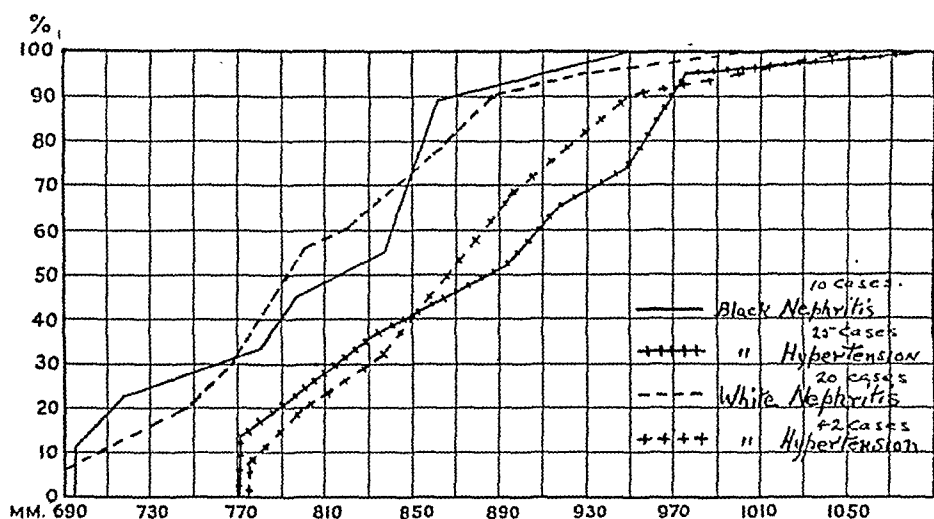


FIG. 4.—Chest circumference.

circumference, present a situation wherein disease group difference overshadows race group differences. In this case the larger thoracic girth of the hypertension people again confirms the general impression of bulk which these individuals had given. Similar graphs could be shown for all the other measurements and indices of the entire body, but space and expense of reproduction make this impossible. Instead, a list of characters and indices is given in which the differences in size or value are simply indicated by plus signs. There is included in this list a column for comparison with the values which were reported for the original series of nephritis and hypertension.⁶ The list follows:

	Hypertension.	Nephritis.	Previous.
<i>A—Head and Face:</i>			
Cephalic length	+	—	=
Cephalic breadth	○	○	=
Facial diameter	+	—	=
Bigonial diameter	++	+	+
Facial height	+	—	—
Nasion prosthion	±	—	=
Nasal height	±	—	=
Nasal breadth	±	—	=
Id. ment.	++	—	=

(This measurement in white hypertension females is equal to that of male gastric ulcer.)

	Hypertension.	Nephritis.	Previous.
Mandible length	++	—	—
Asc. ram. length	+	—	—
Hor. ram. length	++	—	=
Gonial angle	+	—	—
Interpupillary space	+	—	—
Palpebral length	+	—	=
Palpebral breadth	+	—	=

(Has this wide slit relation to hyperthyroidism?)

B—Extremities and Linear Segments:

Finger length	+	—	=
Hand length	++	—	=
Palm length	++	—	=

(White nephritis group of origin G. B. group.)

Span	+	—	=
Vertex (standing height)	+	—	=
Neck height	○	○	=

(The nephritis-hypertension group original series had short necks.)

Sternum length	+	—	=
SSN—AIS	±	—	=
XU-UP	○	○	Hyperten.-neph. group.

Humerus	+	—	—
Radius	+	—	=
Femur	+	—	=
Tibia	+	—	=
Thor. lat. diam.	+	—	=
Trunk	+	—	=
Upper extremities	+	—	=
Lower extremities	+	—	=
Subcostal angle	—	+	=
Chest circumference	+	(both races) —	=
Thor. A. P. diam.	+	—	+

(but hypertension is flatter than flattest of original series.)

Bi-iliac diam.	+	—	=
Bi-acromial diam.	+	—	=
Neck circumference	+	—	—
Weight	+	—	—
Facial index	+	(longer and narrower)	=

Upper facial index	○	○	=
Nasal index	±	—	=
Palpebral index	Reflects wide fissures.		
Bi-acromial Stat. I	—	±	=
Int.-pupillary space nas. pros. I	○ white	±	

(reflects wider fac. diam. of hypertension, int.-pupillary space being.)

Hand I.	—	±	
Thor. L. D. Ch. L.	+	—	
Bi-acromial Stat. I.	—	+	
Chest circ. Stat. I.	±	—	
Thor. L. D. Ch. L. I.	+	—	+
Ponderal index	+	—	

Thus, all the measurements about the head and face show that the hypertension group have larger and heavier skulls and mandibles than the nephritis group. Furthermore in all linear segments, and particularly in the long bones, hands and fingers, greater length

is found among those with hypertension. The same circumstance is true for the girth of the chest. Now, while these findings satisfactorily support the observations of Doctors Studdiford and Herrick, they assume greater interest when considered in the light of our knowledge of acromegaly. Keith⁷ has pointed out that the increase in bony growth in this disease follows definite and constant lines, though there may be more or less variation in its extent. In addition, he makes it clear that these enlargements take place exactly along the path of normal growth. Especially interesting are his demonstrations of the enlargements of the skull and mandible. For example, not only is the cephalic length increased in acromegaly because of the great frontal bosses and the growth of the posterior occipital protuberance, but the mandible develops added length in both ascending and horizontal ramii with a widening especially of the latter. This last increment results in a greater value for the inferior dental-menton distance. Now it is particularly interesting to observe that our measurements of the skulls and mandibles of the hypertension group of pregnancy toxemias show definite increases along precisely the same lines as those described by Keith as characteristic of acromegaly. Furthermore, the greater length of all linear segments, chiefly of the long bones, are, like the acromegaloid characters of the face, indications of a state which when exaggerated has been termed gigantism. Cushing⁸ and others have pointed out that when the pituitary gland is overactive or unrestrained by other influences, before epiphyseal closure, gigantism results. More recently Evans⁹ has shown the powerful growth-stimulating qualities which lie in the anterior lobe of the gland. There are, moreover, certain other remarkable physiological phenomena which are interesting in this connection. For example, that there is a definite checking influence which the gonads exert upon the growth-stimulating qualities of the pituitary is well recognized. Tandler and Grosz, in addition, have had the opportunity of studying the pituitary gland in castrate Skopsi. The gland was found by these observers to be considerably increased in size in these cases. During pregnancy also there are hypertrophic changes in the gland. These may be accompanied, as described by Cushing,¹⁰ by indications of increased activity in one or more of the various fields wherein the pituitary gland functions. As the gland alternates under the recurring stimulus of pregnancy between hypertrophic change and involution, unusual opportunity is provided for distortions of function. For, as Cushing says, "It is readily foreseen, therefore, that ultrafunctional transitions with some manner of secretory perversion may be easily acquired . . . and the transitory clinical manifestations of glandular overactivity already mentioned may persist or even increase after the termination of the pregnancy." Obviously then in the course of pregnancy one may expect not only hyperplasia but hyperactivity of the pitui-

tary gland. And it must not be forgotten that among its many qualities, it possesses a powerful pressor substance. Not only in pregnancy, however, but following castration and its physiological analogue, the menopause, there is hypertrophy with overactivity of the pituitary. The hypertensions of women at this stage of life are common enough.

It must not be inferred from the foregoing discussion of the disturbed physiology of the pituitary gland, that its increased activity in pregnancy is here being held responsible for the existing enlargements of bony parts disclosed by our measurements. The acromegaloid and gigantoid skeletons found in the Sloane cases simply bespeak the end result of a vigorous pituitary influence which acted much earlier during the growth period.

But the suggestion is advanced that such a vigorous gland, whose witness for high functional efficiency is the presence of acromegaloid and gigantoid insignia, may be driven by the conditions of pregnancy to far greater potency of action than an initially less powerful organ. Thus it would appear that the possession of a perhaps large and surely very active pituitary gland, which had assisted in the production of a massive frame, may actually hold a menace for the pregnant woman.

While it is not the purpose of this paper to enter upon a discussion of the mechanism of the nephritides and hypertensions which are not associated with pregnancy, yet attention must be called to the striking similarity of the measurements and indices here reported to those presented for that group in the author's book on *Human Constitution*. In that communication the statement was made that the women of the hypertension-nephritis race were larger women in comparison with women of all other disease races. At first the combining of hypertension cases and nephritis cases in one group was undertaken with considerable hesitation. But it is rather significant that when the figures from the two types of pregnancy toxemia were analyzed, it was found that the nephritis group was composed of individuals who appeared simply to be slightly smaller reproductions of the hypertension-type design.

Conclusions. 1. The original contention of the observers at Sloane, that the hypertension people were larger, heavier, more masculine types than the nephritis people, is borne out by anthropometric studies.

2. The changes or increases in the bony skeleton are precisely along the line of increase found in acromegaly or gigantism.

3. Women of a certain constitutional type, whose skulls, mandibles and skeletons display the insignia of a previously increased activity of the pituitary gland, may under the specific stimulus of pregnancy develop hypertension or nephritis, either transient or permanent.

4. The closeness of the two groups in morphological characters

and their approximation to the combined hypertension-nephritis series suggest that idiopathic hypertension and nephritis are different expressions of one and the same disease.

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OBSERVATIONS ON THE DIAGNOSIS OF SUBPHRENIC ABSCESS.

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ALTHOUGH a considerable literature exists on the subject of subphrenic abscess, and although the condition has been capable of clinical recognition since Leyden,¹ in 1880, described the process, its symptoms and its signs, still the diagnosis of subphrenic abscess is often obscure and almost always difficult until such a time as the condition has become well established. Therefore, it has seemed worth while to discuss this interesting disease, and to cite certain matters germane to its diagnosis which have come to my attention in the observation of a series of cases.

Previous to Leyden's description, subphrenic abscess was of pathologic interest only. Leyden's study first made it possible for the condition to be recognized clinically. Since then the studies of Maydl,² Piquand,³ Barnard,⁴ Elsberg,⁵ Lockwood⁶ and others have contributed much to the understanding of this always insidious and often serious condition. Many other lesser studies and case reports are to be found in the literature; but even yet subphrenic abscess frequently remains unrecognized for long periods of time. The reasons for this will be apparent in the course of the discussion.

Anatomy. In order to understand the formation of subphrenic abscess it is necessary to be conversant with the relations of the diaphragm to the structures and organs below it. The space below

the diaphragm may be divided anatomically into six areas: The right and left extraperitoneal spaces, the right anterior intraperitoneal space, the right posterior intraperitoneal space, the left anterior intraperitoneal space, and the left posterior intraperitoneal space.

The right extraperitoneal space is that area uncovered by peritoneum between the folds of the coronary ligaments as they are reflected onto the diaphragm. The left extraperitoneal space lies above the upper pole of the left kidney, where the peritoneum is reflected onto the diaphragm.

The right anterior intraperitoneal space has the diaphragm and the liver below it. To the right is the falciform ligament; behind, the space extends to the right lateral ligament of the liver. This area connects with the right posterior intraperitoneal space and also with the lumbar fossa which lies between the ascending colon and the loin, the so-called pericolic groove, which gives a direct connection between this space and the region of the cecum and of the pelvis. Because of this connection, abscess is most common in this space, and it may be considered as the only true subphrenic space on the right side.

The right posterior intraperitoneal space is bounded to the right by the abdominal wall; in front by the liver and gall bladder; posteriorly, by the upper pole of the right kidney and the crus of the diaphragm. It is connected with the left intraperitoneal space, which is in reality the lesser peritoneal cavity, by the foramen of Winslow. Infection in the lower abdomen may gain access to this space through the lumbar fossa; on the other hand an infection in the lesser peritoneal cavity may enter this space through the foramen of Winslow.

The left anterior intraperitoneal space is surrounded by the falciform ligament, the stomach and the spleen, with the diaphragm above, and extends as far backward as the left lateral ligament of the liver. The floor of this space is formed by the tail of the pancreas and by the left kidney. While there is no direct connection between them, this space is only lightly shut off from the right posterior intraperitoneal space, and it is connected with the lower abdomen by the left lumbar fossa.

The left posterior intraperitoneal space is analogous to the lesser peritoneal cavity. It is important to remember that part of the boundary of this space is formed by the posterior wall of the stomach and of the duodenum. As has been said before, there is free connection between this cavity and the right posterior intraperitoneal space through the foramen of Winslow. These anatomic connections and surroundings indicate how readily infection situated in the abdominal or retroperitoneal viscera may be carried to one of the subphrenic spaces, and thence by these intimate connections to other regions below the diaphragm.

Etiology. Most subphrenic abscesses are due to infection following acute inflammation or perforation of one of the abdominal viscera, either before or after surgical intervention. A few occur from direct extension from an abscess adjacent to one of the subphrenic spaces, such as a perinephric abscess. More rarely subphrenic abscess is caused by infection through the blood stream from a more distant focus. Lee⁷ has reported 4 cases which were apparently spontaneous in origin. The infection may originate in the thorax and spread downward to the subphrenic spaces, but this is uncommon.

By far the most common sources of subphrenic abscesses are: (1) Appendicitis, (2) ruptured gastric ulcer and (3) ruptured duodenal ulcer. Statistics vary as to which of these conditions is the most frequent cause, but it is generally believed to be the appendix. Abscess of the liver, either amebic, from an infected hydatid cyst, or from an ordinary pus infection, gall bladder disease, abscesses of kidney, spleen or pancreas, have all been described as etiologic factors. Right subphrenic abscesses usually follow appendicitis, liver or gall bladder disease, or are of duodenal origin; whereas, abscesses under the left diaphragm usually follow disease in the stomach, pancreas or spleen. It is interesting to note, however, how many left-sided subphrenic abscesses follow disease of the appendix.

The method by which infection reaches the subphrenic spaces is: (a) By direct extension from a localized or general peritonitis; (b) by the blood stream through the portal vein, or through the arteries, as in general infection; (c) by the lymphatics. The lymphatic connection between the subphrenic spaces and the abdominal viscera is threefold:

1. The retroperitoneal cellular tissue.
2. From around the deep epigastric artery to the falciform ligament, which is in close association with the lymphatics of the appendix and colon.
3. The subphrenic lymph spaces which pass through the diaphragm connecting with the subpleural plexus of lymphatics. While the march of the infection in these cases is usually from the subphrenic space upward through the diaphragm, it sometimes occurs from the pleural cavity downward.

The subphrenic abscess may contain pus alone, which is usually foul, and not infrequently contains gas as well as pus. It is believed that the gas is almost always due to bacterial action. Rarely air may enter the subphrenic space through a permanent fistula connecting it with a hollow viscus.

Symptoms and Signs. In most cases a history suggesting a gastric or duodenal ulcer, gall bladder disease or appendicitis can be obtained. The actual onset of the subphrenic abscess may be either acute or insidious. It is usually insidious following some

acute inflammatory disease of the abdominal organs or the rupture of a hollow viscus. More commonly it follows an operation for some such condition. It has been estimated that almost 1 per cent of appendicitis, which has caused abscess or rupture of the organ, is complicated by abscess beneath the diaphragm.

The course of the condition in these cases is usually as follows: After the operation for the relief of the acute condition, convalescence starts normally, then after a longer or shorter period of time the temperature begins to rise again, and it is evident that all is not well. The temperature rises daily and is of a septic type, varying several degrees in the twenty-four hours. The pulse becomes rapid in proportion to the fever, but the respirations are not usually increased in rate. This fact may be of some importance in the diagnosis. The patient complains of pain, the location of which will depend to some extent on the location of the abscess. If the abscess be in the left or right anterior intraperitoneal spaces, the pain will be referred to the upper abdomen and also will be referred along the distribution of the phrenic nerve, owing to the irritation of the diaphragm. This pain will manifest itself along the upper border of the trapezius muscle, or in the side of the neck. If the abscess be in one or the other of the posterior spaces the pain may be referred to the loin or to the region of the scapula. Hiccough due to diaphragmatic irritation is said to occur in about 50 per cent of the cases, though in the cases to be reported hiccough did not occur in a single instance. Vomiting is not uncommon. As the condition advances the patient develops chills and sweats, and presents the characteristic appearance of an individual suffering from a retained septic process. Emaciation is usually rapid and marked. As the abscess grows larger the condition grows worse, and after a period of time, if proper treatment is not instituted, the infection spreads upward through the diaphragm, causing involvement of the pleural sac, which leads to the effusion of fluid and later to empyema, to infiltration of the lung or to abscess of the lung. When this has occurred, respiratory symptoms, such as cough, dyspnea and pleural pain, will be added to those which already exist. If no treatment is instituted the abscess may rupture through the lung, into the stomach, or into the intestine, and may heal spontaneously.

The physical signs will depend to a certain extent on the location of the abscess, the duration of the process and on the presence or absence of gas within it.

The motion of the chest on the affected side will be limited, and the more the diaphragm encroaches on the chest cavity, the more marked will be the limitation of motion. In late cases where there is secondary involvement of the pleural cavity with effusion, limitation of motion will be great. Theoretically, the movements of the costal margins should be of help in the diagnosis of subphrenic

abscess, but this sign cannot be depended upon in all the cases. Hoover⁸ has shown that when the diaphragm is displaced upward it is at a mechanical disadvantage in exerting its pull on the costal margin, and, therefore, under these conditions the costal margins will move away from the midline to a greater degree than normal. In the 6 cases of subphrenic abscess which I have observed, movements of the costal margin were consistent with a high position of the diaphragm in but 3 of them. In 1 of these cases the abscess was on the left side; in the other 2 the abscess was presumably in the right extraperitoneal space. In the other 3 cases the costal margin did not move at all. In these cases the abscess was on the right side, and presumably involved the right intraperitoneal space. In 1 of these cases autopsy showed the liver so firmly adherent to the costal margin as to make any movement of the costal margin impossible. It is interesting to note that the right anterior intraperitoneal space is the most common spot for subphrenic abscess to begin, and also that the liver is always adherent to the inner side of the costal margin when infection is set up in this space.^{4,6} For this reason the absence of the characteristic action of the costal margin cannot be taken as evidence against a subphrenic abscess. When the costal margin is found to flare more than normally the sign is of distinct diagnostic importance.

There may be localized bulging, depending upon the position of the abscess. The epigastrium may bulge, and the bulging may increase or decrease with the change of position of the patient. This change is due to the action of gravity upon the fluid within the cavity.

Palpation may reveal deep tenderness over the upper abdomen, or in the loin.

Percussion will show dulness over the chest on the affected side; sometimes the dulness is but slight. Later it will become marked and extensive. If there be gas within the abscess there will be an area of tympany which shifts with change of position. Below this area of tympany will be found an area of flatness corresponding with the fluid level within the abscess. In one of my cases dulness in the lower right chest gave way to tympany on change of position. Over the chest on the affected side the breath sounds are usually diminished, as is the vocal and tactile fremitus. Later, as the process extends upward into the lung or pleura, the breath sounds may be characteristic of fluid in the chest, and if the lung itself is involved, rales and bronchial breathing may be heard. The presence of a succussion splash heard over the suspected area is of the utmost importance, as it can mean but one thing—the presence of air and fluid. In 1 of my cases a left-sided abscess, a succussion sound synchronous with the heart beat was heard just below the heart. On fluoroscopic examination, the fluid could be seen to be rhythmically agitated by each heart beat. As far as I

can find out, from a review of the literature, this is the first time that this interesting auscultatory sign has been noted in left-sided subphrenic abscess. A friction rub over the lower chest is not uncommon, and usually means that extension into the pleural cavity has begun.

The heart is rarely, if ever, displaced either to the right or to the left—a point which is of importance in differentiating the condition from effusion into the chest cavity. In large left-sided abscesses the heart is displaced upward.

The position of the liver should be noted. Theoretically the liver should be displaced downward, especially when the abscess is on the right side. But, as has already been pointed out, in right-sided abscesses the liver is frequently adherent to the lower costal margin, and, therefore, cannot be displaced downward. The absence of a low position of the liver, therefore, cannot be taken as evidence against a subphrenic abscess.

When a subphrenic abscess is suspected, examination with the Roentgen ray should always be made. When the patient's condition allows, both fluoroscopic examination and films should be made, and to be entirely successful examination should be made with the patient in the erect posture. If there be a subphrenic abscess the diaphragm will be found to be in a higher position than normal, and often acutely arched. There may be only slight upward displacement in early cases, but as the process increases the diaphragm may be found as high as the level of the third rib. The fluoroscope reveals always a loss of motion of the diaphragm on the affected side, a finding which is of the utmost importance in differential diagnosis.

Case Reports. The following cases have been observed during the past four years:

CASE I.—J. B., a man, aged twenty-eight years, was admitted to St. Alexis' Hospital with an acute appendicitis. At operation a gangrenous retrocecal appendix with a beginning peritonitis was found. After the operation the patient made good progress for a period of four weeks, after which the temperature began to rise. A week later the temperature was 103° C.; pulse, 150; respirations but 20. The patient was very sick, and dulness and rales were found at the base of the left lung. The signs in left chest increased steadily, and the patient grew slowly worse. Four weeks after the onset of the fever the condition was as follows: The patient was emaciated and very ill; the temperature was 103°; pulse, 150; respirations, 30. The upper left chest lagged. The left costal margin flared more than the right. From the sixth rib in the axilla, and at the same level in the back, there was marked dulness, with absent vocal and tactile fremitus, and distant breath sounds and numerous moist rales. Over the ensiform cartilage, and just below the apex of the heart, there was a metallic tinkling succussion sound synchronous with the heart beat. There was also a marked succussion splash heard over the left axilla. The fluoroscopic examination showed the left diaphragm 3 or 4 inches higher than normal, and acutely arched. There was no excursion of the diaphragm; a large collection of gas was seen below the diaphragm, and below

this a fluid level which was thrown into waves by the heart's action and when the patient was shaken. The costophrenic angle was hazy, and there was evidence of infiltration in the base of the left lung.

Operation revealed a large collection of pus below the left diaphragm, which was drained. The patient died two days after the operation.

Comment. The points of interest in this case were the occurrence of subphrenic abscess on the left side following an appendicitis and the presence of the very unusual succussion sound when the heart's action agitated the fluid below the diaphragm. In this case the movement of the costal margin pointed to a high position of the diaphragm.

CASE II.—F. P., a man, aged thirty-four years, was admitted to St. Alexis' Hospital. Ten weeks before admission he had sudden sharp epigastric pain. The pain was relieved by vomiting and by the ingestion of sodium bicarbonate. Since the onset the pain has been more or less constant, recurring at least once daily. On admission the patient complained chiefly of loss of weight and strength. Physical examination showed a sallow, emaciated individual; temperature, 100°; pulse, 80; respirations, 20. The movements of the right chest were limited. The right costal margin moved not at all. Percussion showed flatness from the angle of the scapula downward, from the sixth rib in the axilla and from the fourth rib in the midclavicular line. The dullness shifted with change of position, and the area in front became tympanitic when the patient was lying down. The breath sounds were very distant. A few crackling rales were heard at the base of the right lung. Succussion sound was present. The liver was not displaced downward.

Roentgen ray examination showed the right diaphragm at the fourth rib. Excursion was absent. The costophrenic angle was obliterated. Below the diaphragm was a clear space, below which there was a fluid level which was seen to splash when the patient was shaken. There was evidence of infiltration in the base of the right lung.

A diagnosis of right subphrenic abscess resulting from a gastric or a duodenal ulcer was made. The patient refused operation. However, he returned to the hospital a month later, at which time the abscess was opened and drained. The patient made a complete recovery.

Comment. It is interesting to note that in this case the onset was insidious; also that the costal margin moved not at all and that the liver was not pushed down. It is fair to suppose that in this case the liver was firmly adherent to the costal margin, as the infection involved the right anterior intraperitoneal space, spreading thence from the lesser peritoneal cavity.

CASE III.—M. F., a girl, aged thirteen years, was admitted to St. Alexis' Hospital with a ruptured gangrenous appendix, and was operated on immediately. Her progress was satisfactory until three weeks after the operation, when the temperature rose to 102° and continued to show a daily rise from then on. Four weeks after admission the condition was as follows: The motion of the right chest was greatly limited; the right costal margin moved not at all; percussion showed dullness from the third rib in the midclavicular line which extended to the axilla and back. The breath sounds were very distant. The vocal and tactile fremitus were much diminished. A small pleural friction rub was heard just below the right nipple; there was no succussion splash. The liver was not displaced downward. Roentgen ray examination showed the right diaphragm at the upper level of the fourth rib; the excursion was absent; the costophrenic angle was hazy, but the lung was clear (Fig. 1). A diagnosis of subphrenic



FIG. 1

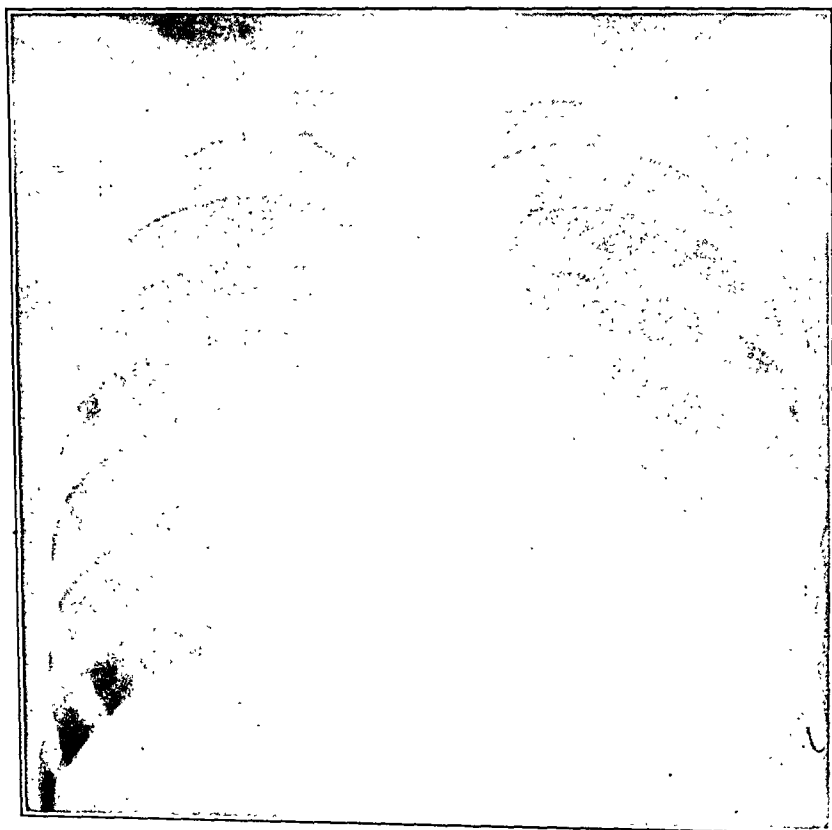


FIG. 2



FIG. 3

abscess was made tentatively, but it was not deemed wise to operate at this time. The signs in the chest continued to increase, and several days later another examination with the Roentgen ray showed that while the diaphragm remained in the same position as formerly, there was a mottled density in the right lower lobe, and also evidence of fluid in the costophrenic angle (Fig. 2). Evidences of an increasing amount of fluid in the right pleural cavity appeared, and several days later a third Roentgen ray examination showed that the line of the diaphragm could no longer be seen, and that there was evidence of a well-marked effusion in the chest (Fig. 3). A diagnosis of subphrenic abscess, with extension upward into the pleural cavity and the lung was made. Both the pleural cavity and the subphrenic space were drained. Serous fluid was obtained from the chest cavity and foul pus from below the diaphragm. After the operation the patient made a complete recovery.

Comment. The accompanying illustrations (Figs. 1, 2 and 3) demonstrate clearly the advance of infection in the thorax, once it has been carried upward through the diaphragm. It is presumable that in this case the liver was adherent to the costal margin, because the liver was not displaced downward, nor did the right costal margin move on inspiration.

CASE IV.—W. C., a male, aged thirty-five years, ten days before admission to St. Alexis' Hospital, had a very severe pain in the epigastrium, associated with vomiting. For four days thereafter he had considerable pain and tenderness in the epigastrium. On the fourth day the temperature rose and the patient became worse. The patient was admitted to the hospital ten days after the onset in the following condition: Motion of the right chest was limited; the right costal margin moved not at all; there was flatness from the third rib in front and from above the angle of the scapula behind. Breath sounds were absent. Tactile fremitus was diminished. There were a few moist rales at the right base. No succussion sound was heard. The liver was not displaced downward. The Roentgen ray examination was unsatisfactory on account of the condition of the patient, which was very serious. Based on the history and findings, a tentative diagnosis of subphrenic abscess was made. Operation was performed, and a great deal of foul-smelling pus was evacuated from below the diaphragm, but the patient died. Autopsy showed a perforated ulcer on the upper curvature of the stomach behind and a subdiaphragmatic collection of pus. The liver was firmly adherent to the costal margin. There was a small amount of pus in the right pleural cavity and a beginning bronchopneumonia at the base of the right lung.

Comment. This case shows several points of interest. The process was unusually acute. Autopsy showed that, as a result of the subdiaphragmatic inflammation, the liver was so firmly and extensively adherent to the right costal margin, that any displacement of the liver downward, or any movement of the costal margin was impossible. Here, again, the readiness with which the pleura and lung are involved is well shown. In this case the infection arose in the left posterior intraperitoneal space and spread thence to the right anterior intraperitoneal space.

CASE V.—A girl, aged eight years, was admitted to St. Alexis' Hospital after having been knocked down by an automobile. She had five fractured ribs on the right side and numerous contusions. Physical examination on admission was negative except for the evidence of trauma, and the patient seemed in good general condition. There was some pain in the abdomen, and a specimen of urine showed blood which on the day after admission had increased in amount. Three days after admission the temperature

rose to 104° and the patient ran a high irregular fever for the next three weeks. There was pain, tenderness and rigidity in the upper abdomen. Three weeks after admission the patient passed a large amount of pus in the urine, following which the temperature came to normal. After a few days the temperature again rose. At this time it was noted that there was limitation of motion over the lower portion of the right chest, and that there was flatness over the right base and in the right axilla, and that the breath sounds were diminished. Also a succussion sound was heard in the right axilla. The costal margin flared away from the midline more than normal, and the liver was displaced downward. Roentgen ray examination showed the diaphragm arched to the level of the third rib. The excursion was absent. Below this there was a collection of gas, with a fluid level below it. On these findings a diagnosis of subphrenic abscess was made, which was confirmed by operation. At operation a large amount of pus was evacuated from below the diaphragm. The abscess was retroperitoneal, and apparently arose in the region of the right kidney. The child made a complete recovery.

Comment. In this case the subdiaphragmatic inflammation was secondary to an abscess located either within or around the right kidney. Apparently, the abscess was confined to the right extraperitoneal space. It is interesting to note that the liver was displaced downward and that the movements of the right costal margin indicated a high position of the diaphragm. Because the abscess was confined to the right extraperitoneal space in this case, the absence of any adhesions attaching the liver to the costal margin can be supposed. This would explain the mobility of the liver and the characteristic action of the costal margin.

CASE VI.—M. I., a woman, aged forty-one years, was admitted to St. John's Hospital, with an appendiceal abscess, symptoms of which had been present for a period of about two months. On admission there was a large mass in the right side of the abdomen, characteristic of appendiceal abscess, but there was no evidence of infection elsewhere in the abdomen or in the thorax. The abscess was drained in the usual manner. After the operation the patient continued to run a septic temperature, varying between 100° and 102.5° daily. The pulse stayed in the neighborhood of 120. The respirations rose gradually, until two weeks after the operation, when they were between 35 and 40 per minute. At this time physical examination showed the following condition: The lower portion of the right chest was fuller than the left; the motions of the right chest were limited. The right costal margin moved away from the midline more than the left. Percussion of the right chest showed dulness from the fourth rib in the midclavicular line, from the sixth rib in the axilla and from the angle of the scapula behind. Over this area the breath sounds were distant and a few moist gummy rales were heard. No tubular breathing, egophony, or succussion sounds were heard. The tactile fremitus over the lower right chest was absent. The heart was not displaced. The lower border of the liver was palpable well below the right costal margin.

Fluoroscopic examination showed the right half of the diaphragm at the fourth rib, acutely arched. There was no respiratory motion of the right half of the diaphragm. No air bubble was seen. Films confirmed the shape and position of the diaphragm, and showed in addition some opacity in the right costophrenic angle. There was no roentgenologic evidence of any infiltration at the right base.

On these findings a diagnosis of right subphrenic abscess was made. Operation was performed immediately, and the abscess found and drained. The patient made a marked improvement for three days, and then had

a sudden rise in temperature to 103° , a chill, cough and prostration. On the fourth day after operation the patient coughed up a large amount of foul pus, after which steady improvement in the condition set in. The cough and expectoration of purulent material continued for about three weeks. The subphrenic abscess drained rapidly and the wound closed normally. The temperature fell gradually and steadily. Four weeks after the recognition of the subphrenic abscess the patient left the hospital convalescent. Four weeks later she was examined again. She had gained weight and strength. While some cough persisted, there was little or no expectoration, and both operation wounds had healed.

Comment. This case illustrates the readiness with which infection spreads from beneath the diaphragm upward and into the chest cavity. Although at the time of the operation for the subphrenic abscess there was evidence only of a very slight process in the right pleural sinus and lung (that is, opacity in the right costophrenic angle in the Roentgen ray and rales low down over the right base). The process in the thorax developed rapidly after the operation, and discharged itself through the bronchi. While it is possible that this discharge was from another subphrenic pocket of pus, which ruptured upward, I think this is highly unlikely in the light of the chest findings prior to the operation, and also because a most careful search for hidden pockets under the diaphragm was made at the time of the operation. The movements of the costal margin and the position of the liver were consistent with a subphrenic abscess in this case. It is presumable that the abscess was not in the right anterior intraperitoneal space, and that therefore adhesions had not formed between the liver and the costal margin.

Discussion. The above cases serve to emphasize the fact that subphrenic abscess is of insidious onset, and that early diagnosis is infrequent. On account of the lack of physical signs pointing directly to the subdiaphragmatic location of the infection, the condition is often confused with some postoperative inflammation within the thorax. In each of the cases reported there was dullness, diminished breathing and diminished or absent fremitus on the affected side; in 5 of the 6 cases adventitious sounds pointing to involvement of the pleura, or of the lung, were noted. These signs naturally draw attention to the thorax as the location of the inflammation of the complication. In only 3 of the 6 cases was the outward movement of the costal margin exaggerated, as would be expected to be the case, were the diaphragm in a higher position than normal. In only 3 cases was the liver displaced downward, as would be expected, when a collection of pus lay between the liver and the diaphragm. Therefore these two signs, which when present are important evidence of subphrenic abscess, cannot be depended upon in all cases. As has been pointed out the anatomic location (that is, the particular subphrenic space) of the abscess will determine the presence or absence of these signs. If the abscess be in a position which will cause adhesions between the anterior surface of the liver and the costal margin, then neither of these signs will be present, because the liver will be firmly fixed and, therefore, cannot be displaced downward; on account of its

fixation to the liver the costal margin is held immobile. The presence of a succussion sound and of shifting dulness should always suggest the presence of subphrenic abscess, but these signs are by no means constant. They were observed in 3 out of the 6 cases reported.

The results of Roentgen-ray examination in these cases are of interest. In all 6 it was found that the diaphragm was displaced upward, was more acutely arched than normal and that diaphragmatic motion on the affected side was lost. The loss of diaphragmatic motion seems to be characteristic of subphrenic abscess. Other conditions which enlarge or displace the liver upward may affect the position of the diaphragm, but in such conditions, while the movements of the diaphragm may be limited, they are not lost. It is reasonable to suppose that this loss of motion of the diaphragm in subphrenic abscess is analogous to the loss of motion ("splinting") of the abdominal muscles in intraabdominal inflammation. Involvement of the pleura and lung may be made out earlier by the Roentgen ray than by physical examination. This is illustrated by the serial observations in Case III. Of course, the value of the Roentgen-ray examination will be vitiated if the process in the lung or pleura be so far advanced as to make a clear observation of the position and of the movements of the diaphragm impossible. While clinical observation and examination should lead one to presume the presence of a subphrenic abscess in all cases, and should enable one to definitely assert its presence in a certain proportion of cases, yet earlier and more positive evidence is to be looked for in the results of the Roentgen-ray examination. Recent articles by Lockwood,⁶ Ullman and Levy,⁹ Cottle,¹⁰ Douglas¹¹ and Le Wald¹² confirm the importance of the Roentgen-ray examination.

Obviously, it is highly desirable to drain the abscess before the structures above the diaphragm are involved. In reviewing the subject, as well as in the cases which have come under my own observation, it is striking to note how seldom a diagnosis is made early enough to accomplish this. An early diagnosis of subphrenic abscess can only be established by constant watchfulness for the appearance of this insidious condition and by repeated clinical and roentgenologic examinations.

Conclusions. 1. Subphrenic abscess is not an uncommon sequel to rupture or inflammation of one of the abdominal viscera.

2. Early recognition of subphrenic abscess is difficult. Its onset is insidious, and its physical signs are frequently confounded with those of intrathoracic disease.

3. The movements of the costal margin and the position of the liver may be misleading, depending upon the anatomic location of the subdiaphragmatic inflammation.

4. The most important and the most definite aid to the diagnosis

is the Roentgen-ray examination. Repeated examinations are of the utmost importance, not only in confirming the diagnosis, but also in observing the course of the disease.

I wish to thank my colleagues, Dr. G. E. Follansbee, Dr. F. J. Gallagher, Dr. F. C. Schmoldt and Dr. J. V. Kofron of the Surgical Service of St. Alexis' Hospital for the opportunity of observing the cases reported in this paper. I am especially grateful to Dr. E. P. McNamee, who made the roentgenologic observations on these cases, for his interest and coöperation.

SUMMARY OF PHYSICAL AND ROENTGENOLOGIC FINDINGS IN SIX CASES OF SUBPHRENIC ABSCESS.

Physical signs observed in 6 cases:	No. of cases present.	Per cent.
Limitation of thoracic movements	6	100
Asymmetry of chest	3	50
Outward movement of costal margin increased	3	50
Outward movement of costal margin absent :	3	50
Percussion dullness	6	100
Breath sounds and fremitus diminished or absent	6	100
Adventitious sounds in lung or pleura	5	83
Succussion sound	3	50
Lateral displacement of heart	0	
Displacement of liver downward	2	33
Roentgenologic findings observed in 5 cases:		
Diaphragm arched and displaced upward	5	100
Movements of diaphragm absent	5	100
Lateral displacement of heart	0	
Subphrenic air bubble, fluid level and splash	3	50
Clouding costophrenic angle	4	80
Infiltration base of lung	4	80

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GENERALIZED TUBERCULOUS ADENITIS WITH REPORT OF A CASE.

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GENERALIZED tuberculous adenitis without other involvement is an extremely rare condition. Following is a case report with a review of the available literature.

History. The patient, F. C., is a nineteen-year-old white male, truck driver, who was first seen on May 17, 1923, when he complained of swelling in front of both ears, under the chin and neck, and a feeling of weakness and loss of "pep." He says he felt well up until about the middle of February, 1923, when he noticed two small masses about the size of a bean in front and below the border of the left ear. There was no pain or tenderness, although the sensation of pressure made him consult his physician. The patient continued at his work for the next two weeks and during this time he gradually noticed increasing fatigue, weakness and loss of ambition. About this time, while accidentally stroking under his chin, he felt small masses in that region also. These were neither painful nor tender, but his general condition became poorer. The swelling started in front of the left ear, then at the right ear, then in the neck. Four weeks after the onset, when examined, he was told that there were similar masses in the axilla, elbows, groins and the back of the neck. These masses kept on increasing in size, reaching the dimension indicated in the physical examination. Following his physician's advice he finally quit working, stayed at home and rested; he drank plenty of milk, and at the time when we first saw him (about two months after the onset) he felt much better, in fact, had no complaints and intended to go back to work.

He lives in Pittsburgh and has been drinking boiled milk supplied by one of the large local dairies. There is no history of cough, expectoration, night sweats, dyspnea or loss of weight, but there is occasional dizziness. Otherwise the history is negative. He has had one attack of tonsillitis, about two years ago.

His habits are good, and he gives no venereal or alcoholic history. He smokes about twenty cigarettes daily and chews about one pack of tobacco per day.

PHYSICAL EXAMINATION. The patient is a young, well-developed, and well-nourished adult, who does not appear acutely ill. He weighs 143 pounds and is 5 feet 8 inches tall. There is a suggestive puffiness of the face. The temperature during the first three

weeks ranged between 98.2° and 99°, usually higher in the evening, while the pulse ranged from 90 to 100. Eyes, ears, nose and throat are negative. The lungs show no changes beyond the normal variations, except for slight impairment over the right apex, and there are no rales. The heart is not enlarged and shows no murmurs. The blood pressure is 110 systolic and 50 diastolic. The pulse is of good volume and regular and the response to effort is good. The spine, abdomen, genitalia and rectum are negative. The spleen is not enlarged. The nervous system shows no involvement; motor and sensory functions and reflexes are normal. The extremities show the presence of numerous small healed lesions, scarlike in appearance, occurring over the flexor surface of both arms. There is no bronzing of the skin, but a suggestion of osteoarthropathy of fingers.

All the external lymph glands of this patient are involved in a generalized enlargement; the glands on the right are somewhat larger than on the left with only a few exceptions. Nowhere is there any pain, tenderness, local heat or sign of inflammation, or suppuration. There is no scarring, no infiltration of the deep tissues, no matting together, no adherence to the skin. The glands are discrete, variable in size, as will be described later, hard and firm, and usually almond shaped. No signs of pressure are caused by these enlargements except perhaps for some impaired percussion over the right apex, probably due to the pressure of the enlarged right bronchial glands. The anterior auricular, postoccipital, anterior and posterior cervicals, submaxillary, supraclavicular, infraclavicular, axillary, epitrochlear, inguinal and popliteal glands were all palpable and enlarged varying in size from 1½ by 1 cm., to 3 by 2 cm.

LABORATORY EXAMINATIONS. The urine was negative throughout. Hemoglobin and red blood cells were normal; the leukocytes, 5600, with a normal differential. The Wassermann was negative. Blood chemistry was normal, as was the electrocardiogram.

The pathological report of excised glands follows: The right epitrochlear gland was first removed. Under low power the section presents a mosaic pattern, which under high power is composed of masses of endothelial cells interspersed with lymphocytes and fibroblasts. An occasional giant cell is found, usually in the center of the group of endothelial cells. The nuclei of the giant cells are placed at one pole. There is no evidence of necrosis. The endothelial cell groups are separated from each other by lymphoid tissue.

The left epitrochlear gland was later removed. The section presents the same picture under low power, but the high power examination differs from the first section, in that the giant cells and fibroblasts are more numerous within the granuloma, and there is beginning encapsulation around each separate tubercle. A diagnosis of tuberculous adenitis was made.

Roentgen-ray examination of the chest on April 9, 1923, by Dr. G. W. Grier was reported as follows: "There is a marked enlargement of the mediastinal glands extending up into the neck. We have never seen tuberculous glands so large or so clearly defined as these. The appearance is more like leukemia or Hodgkin's disease." A second examination on February 9, 1925, showed two glands at the right hilus; there was marked improvement as compared with the former picture.

A tuberculin test was positive. Guinea-pig inoculation with gland material was negative, as were sections of gland stained for tubercle bacilli.

COURSE AND TREATMENT. Soon after the diagnosis was established the patient was placed on high caloric diet and told to stay away from work. He was subsequently seen and treated by Dr. Page, his family physician. Within from four to six weeks he began to feel better, his appetite increased and the temperature came down and remained at the normal level. Gradually, the various glands commenced to decrease in size so that about ten or twelve months after the onset the generalized glandular enlargement disappeared. At present (two years after onset) one can feel several small glands in the posterior cervical region and two in the inguinal region, but no enlargement anywhere else. Patient states he feels absolutely well, is symptom free and has been at his work for some time. The progressive improvement with apparent ultimate cure shown by this patient is not in accord with the prevailing view that generalized glandular tuberculosis is an acutely progressive and fatal disease. The question naturally arises as to whether or not we were here dealing with an infection due to the bovine type of tubercle bacillus.

RÉSUMÉ. The picture presented is that of a young, healthy looking, adult male patient, showing a generalized glandular enlargement, which involved both the external and internal groups of lymph glands; this condition was of gradual onset and of about two years' duration, at first accompanied by slight fever but with no pronounced asthenia, no systemic symptoms, no abnormal blood picture. The glands were discrete, varying in size and there was no tendency to infiltration, no acute inflammation and no suppuration.

DIAGNOSIS. The age, sex, mode of onset, distribution and clinical appearance of the glands, as well as the characteristic involvement of the mediastinum, the negative blood picture, the comparatively slow course, and the exclusion of any of the other more probable conditions, all suggest very strongly Hodgkin's disease. In fact, after studying the case, this was the conclusion reached. And yet, it was felt that because there was no splenomegaly (in 75 per cent of Hodgkin's disease this is found) and because the cervical and mediastinal glands were comparatively not much enlarged, that it might be advisable to excise one of the glands for section. On

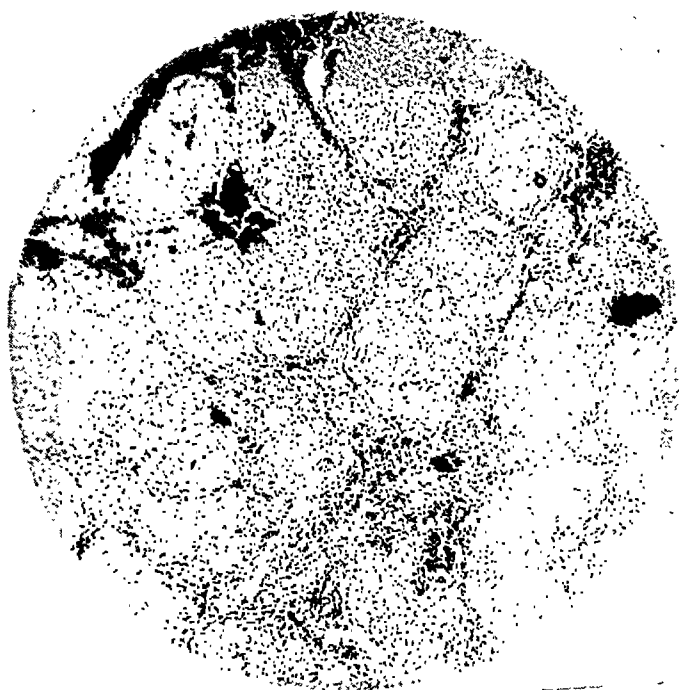


FIG. 1.—Low power photomicrograph of left epitrochlear gland.

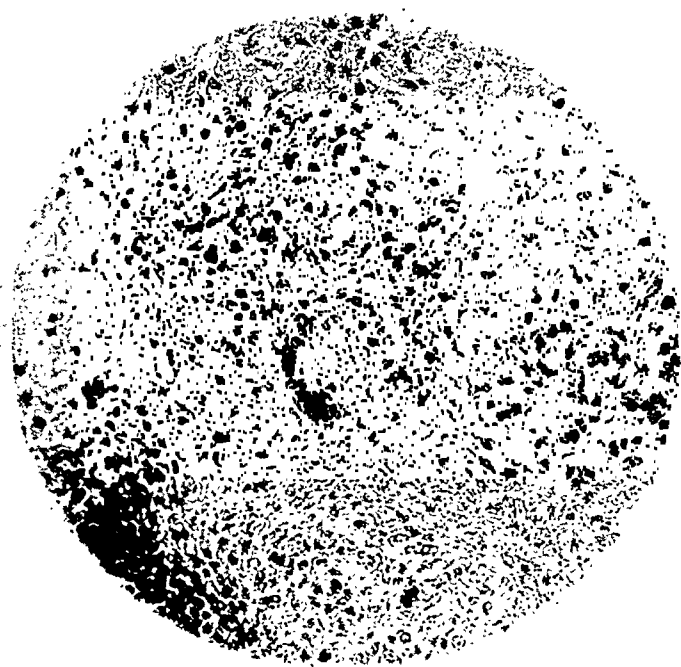


FIG. 2.—High power of section from Fig. 1.

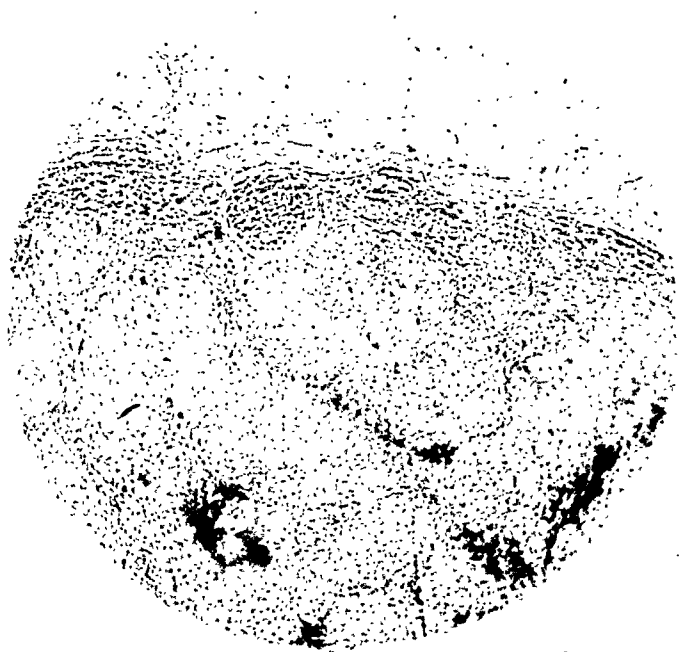


FIG. 3.—Low power right epitrochlear.

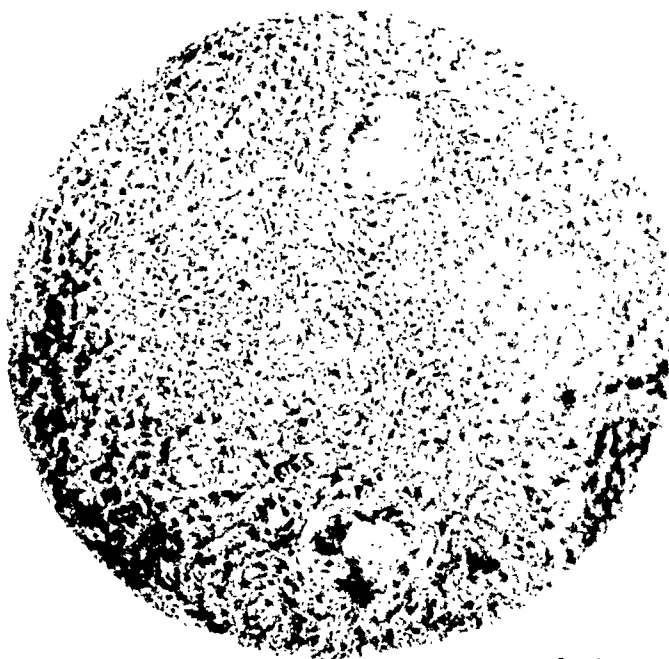


FIG. 4.—High power right epitrochlear.

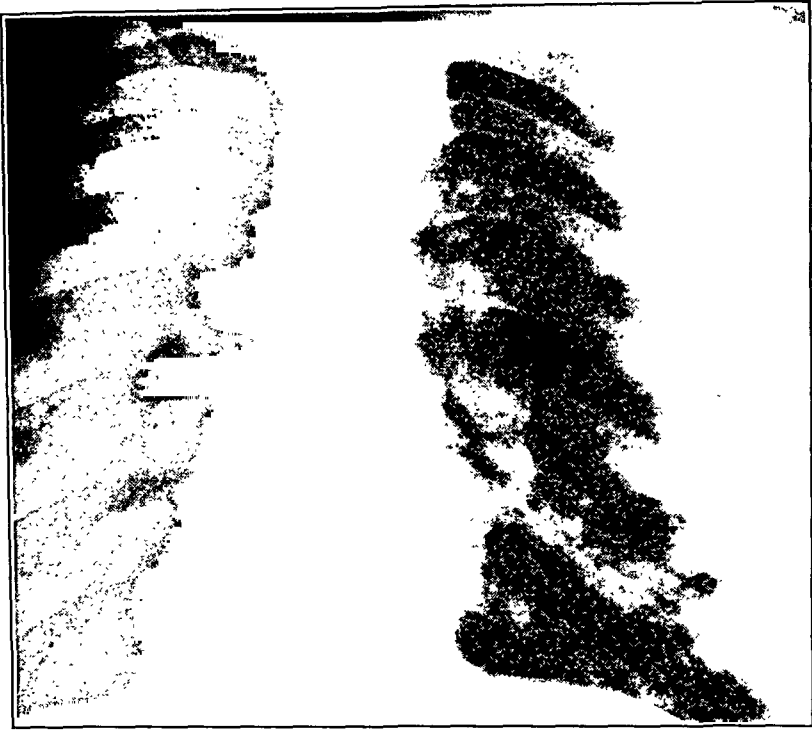


FIG. 5.—Roentgen ray of chest—marked enlargement of mediastinal glands.



FIG. 6.—Marked improvement with diminution of mediastinal enlargement.

doing this, we selected the right epitrochlear in order to exclude some associated condition that might more likely be found if one of the cervicals were sectioned. The sectioned gland showed a picture typical of tuberculosis as given in the pathological report. In order to make doubly certain, another gland was excised with the same result. Guinea pigs were inoculated with this gland with the idea of demonstrating whether one was here dealing with bovine or human tuberculosis.

Comment. A review of the available literature discloses but few such genuine cases. Most of the reports are meager and more or less confusing: (1) Because the generalized adenopathies have not been recognized as clinical and pathological entities until fairly recently; and (2) because the confusion that existed and still exists as to the etiology of some of these adenopathies still raises the question of entity. The few reports of such cases are not conclusive in that they are not accompanied by biopsy or bacteriologic studies.

It was not until 1845 that Virchow described the blood picture in leukemia, making possible the separation of this disease from other forms of adenopathies. Hodgkin, in 1832, described the glands of the disease which now bears his name, and, for some time since, the question has often been raised as to the relation of this condition to tuberculosis. In fact, clinically at least, generalized tuberculous adenitis is not infrequently diagnosed as Hodgkin's disease. Delafield¹ reported a case of general adenitis which clinically resembled Hodgkin's disease but which at autopsy was found to be one of general tuberculosis involving the lungs, spleen and various groups of lymph nodes. Sternberg in 1898-1899 reported on 13 autopsied cases of Hodgkin's disease, 8 of which proved to contain tubercle bacilli.

Sailer,³ (1902) from an investigation of the literature, was unable to find any clinical features to distinguish between tuberculous adenitis and Hodgkin's disease, and thought that the entire evidence tended to confirm the supposition that the majority of cases of Hodgkin's disease, if not all, would be ultimately recognized as tuberculous in nature. However, Andrews,⁴ in the same year, concluded that while there is a form of tuberculosis of the lymph nodes clinically indistinguishable from Hodgkin's disease (lymphadenoma) yet, Hodgkin's disease is a separate entity not due to the tubercle bacillus. He further brings out the point that histologic and bacteriologic procedures can always settle the question and that a fair number of patients with Hodgkin's disease become secondarily infected with tuberculosis.

This confusion is now almost extinct as a result of the conclusive studies of Reed⁵ and others who established the fact that Hodgkin's disease bears no relation to tuberculosis. The entire discussion is of interest because this case as well as one other case reported was clinically diagnosed as Hodgkin's disease and only after histologic studies was the diagnosis of tuberculous adenitis made.

Sabrazes,⁶ in 1892, and later Ducion, first demonstrated that it is possible to have generalized adenitis due to tuberculosis: Berger and Besancon in 1899 dealt again with such a type of glandular enlargement, supporting the writings of Schurr, of Vienna, and Tixier Courmont, and Bonnet.⁷ But of actual case reports there are but few which present no evidence of visceral tuberculosis.

Tedenat,⁸ in 1901, reported the case of an eighteen-year-old male who presented enlarged maxillary, cervical, axillary and iliac glands, verified as tuberculosis by section and inoculation. There was no evidence of tuberculosis in the lungs. In the same paper he reports another case, that of a forty-year-old Italian workingman with enormous glandular masses in the epithrochlear, cervical and all other glandular regions of the body, this condition being accompanied by fever. The patient died in six months and section proved the glands to be tuberculous. Nothing, however, is said about the presence of tuberculosis elsewhere. Delafield, Weisshaupt⁹ and Askanazy report similar cases but in none is the evidence convincing as to the absence of tuberculous lesions in any of the other organs. Patton¹⁰ reports from the Cook County Hospital the case of a patient who started with a generalized glandular enlargement, fever, cachexia and few rales in the apices of both lungs. The disease had an acute course and autopsy showed tuberculous involvement of all glands in the body as well as of most of the organs. Goodhart¹¹ reports another similar case, of acute onset, rapid development and fatal termination. Autopsy, however, revealed tuberculous involvement of many of the organs in addition to the entire glandular system. Buicliu¹² and others likewise report cases showing generalized adenopathy of tuberculous origin, but, invariably, associated with tuberculosis elsewhere. Williamson¹⁴ reports the case of a young nurse who was taken ill suddenly, with fever, malaise and enlarged glands, in the cervical, axillary and inguinal regions as well as some enlargement of the internal group, chiefly the abdominal glands. The course was rather acute and stormy, but after nine weeks of high fever and illness, the temperature began to fall, the glands to diminish in size, and finally became so small that they were not palpable and the patient got well. Biopsy proved the glands to be of tuberculous nature of the bovine type.

The question then arises, what is the relationship between visceral and glandular tuberculosis? Why is it that the glandular system alone will, as in this case, become involved, and what is the method of transmission in these cases?

Regional tuberculous adenitis usually follows on tuberculosis of the organ or organs drained by the lymphatics involved, as mesenteric tuberculosis secondary to tuberculous enteritis. However, tuberculous cervical adenitis is not uncommonly seen without demonstrable primary tuberculous site. It is also true that tubercle bacilli may be engulfed by phagocytes and carried to neighboring

lymph nodes without demonstrable lesions in the viscera. This is one explanation for the frequency of peribronchial tuberculous adenitis without any lesions in the lungs, as seen in this case. In regional tuberculous adenitis it is conceivable that the bacillus may have as its portal of entry the regional mucous membranes or the skin. However, in generalized glandular tuberculosis this explanation does not hold, for, we are here dealing with a systemic involvement for whose dissemination the lymphatic supply or the blood alone can be held responsible.

We know that the tubercle bacillus is conveyed from one part of the body to the other by the blood or lymphatics. How is it then that during this spread none of the viscera will at times become involved? In attempting an explanation one is naturally driven to the conclusion as to the possibility of selective affinity of the tubercle bacillus for certain tissues. Thus, it is argued, *Treponema pallidum* has been shown to early invade the blood stream and likewise to show affinity for certain tissues, so that, there are patients who show cutaneous manifestations of their infection, while others show visceral, vascular or nervous involvement. Therefore, may it not be possible that varying strains of tubercle bacilli may also have such a selective affinity? The evidence in favor of this supposition is not conclusive.

Tixier, Courmont, Bonnet⁷ and others have shown experimentally that guinea pigs injected with material from glands of patients suffering with generalized glandular tuberculosis lived longer than guinea pigs injected with material from the tuberculous meninges of the same patient. Not only that, but the first injected guinea pigs were shown to develop generalized tuberculous adenitis, whereas the second developed tuberculosis of all organs. They seem, therefore, to deduct (1) the presence of a selective affinity, and (2), that glandular tuberculosis is not anywhere near as virulent. However, difference in virulence of tubercle bacilli had never been very clearly demonstrated. This work has not been confirmed by others. Not only that, but Tedenat and his co-workers deduce from clinical experience that generalized glandular tuberculosis is usually fatal. With this opinion Fagge¹³ and Goodhart¹¹ agree. The clinical course of the case here reported does not confirm this view.

Summary. 1. A case of generalized tuberculous adenitis without any visceral tuberculosis is here reported. The condition is getting progressively better and is of two years' standing.

2. Clinically the condition may easily be confused with Hodgkin's disease but biopsy and bacteriologic study will settle the diagnosis.

3. A review of literature discloses but few such cases.

4. There is no explanation as to how the glands may become involved in such process without any visceral involvement.

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SPONTANEOUS RUPTURE OF THE HEART.

A CLINICOPATHOLOGIC STUDY BASED ON 22 UNPUBLISHED CASES AND 632 FROM THE LITERATURE.*

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SPONTANEOUS rupture of the heart is of sufficient rarity to occur but seldom in the experience of a single individual; its dramatic qualities are such, however, that the individual frequently wishes to record his experience, with the result that medical literature contains a comparatively large number of single cases or small group reports. This, together with the coincidence of several cases within a short period at the Philadelphia General Hospital has led us not only to present in detail 22 hitherto unpublished

* We take this opportunity of expressing our thanks to Drs. A. J. Smith, J. Eiman and J. R. Paul for the material they have offered us and especially to Dr. S. B. Wolbach for the series of 9 unreported cases from the Peter Bent Brigham Hospital.

cases that could be collected from this and other hospitals of Philadelphia, but also to tabulate the important items of 632 cases from the medical literature of the past fifty years. The incidence of only 7 cases in 16,000-autopsies at the Philadelphia General Hospital is similar to that reported by Romeik at Munich (7 in 13,000 autopsies), but less than the Leipzig series (9 in 8000 autopsies).

The beginning of our search was made with the year 1872. Except for a few cases of historical interest, it was felt that cases prior to 1872 would not have been studied in a sufficiently modern way to fit in with the analysis of the later cases. In 1872 Quain published his important article "On Fatty Diseases of the Heart," which not only presented data on a large series of hearts that had ruptured, but also announced principles that dominated the thought on this subject for many years. In fact some of his statements, misleading rather than incorrect, and hardly possible to have been improved upon in the state of cardiac pathology of that day, are responsible for some of the mistaken views that are held on the subject of cardiac rupture today. Quain was correct in asserting that "Rupture of the heart may be said never to occur spontaneously when the heart is healthy." Accurate on the whole is his description of the appearance of the tear, its relative frequency in the various chambers and in the two sexes, the importance of old age and of most of the symptoms observed. His description of the pathogenesis and the myocardial lesions, however, was very unsatisfactory. Twenty-seven per cent were considered to be due to fatty degeneration and 6 per cent to softening. Ulceration, interstitial hemorrhage, abscess and bursting of an aneurysm were also mentioned, while the coronaries were barely noticed. In modern textbooks of pathology such statements occur as "The most frequent causes are fatty degeneration of the muscle and occlusion of the coronary arteries, less commonly, myomalacia, abscess, gumma echinococcus cysts and new growths are responsible." One of the best pathological textbooks states that spontaneous rupture usually occurs with chronic aneurysma cordis, necrosis following coronary disease, marked fatty infiltration, especially if combined with fatty degeneration or brown atrophy; the latter an obvious "left over" from the days in which the condition of the coronary arteries was seldom reported upon and their significant relation to myocardial lesions apparently not well understood. In the present analysis particular attention is paid to this point, which has also been emphasized by Robin and Nicolle.

Methods. During the past fifty-two years there have been valuable summaries of this subject by Minet and Le Clerc, based on a study of 77 cases; by Robin and Nicolle, based on 177 cases; Quain's 100 cases previously mentioned. These together with the 22 cases of our own series and the 278 cases analyzed by us from the literature make a group of 654 cases on which this study has been based.

Valuable summaries by Elleaume and Barth had to be omitted from our figures, as it was probable that some or many of their cases had been used by Robin and Nicolle. As the latter's cases were tabulated as individuals, we were able to compare them with our lists and thus eliminate 26 duplicates. As Quain's list may also contain some duplicates, though probably few, we have preserved the identity of the main sources in our tables. Thus the reader may select as he chooses, as well as compare the various sources. The 278 cases that we have abstracted from the general literature were secured from 191 references in the *Index Medicus* and the *Index Catalogue* of the Surgeon-General's library.* In each case, as far as possible, information was tabulated about the sex, age, occupation, habits and past history, clinical diagnosis, onset of duration of severe cardiac symptoms, symptoms attributable to the rupture, duration of life after probable occurrence of rupture, whether or not it happened during sleep, if hemopericardium was present, site, size, nature of tear in the myocardium, whether partial or complete, cause of rupture, contributing lesions, condition of coronaries and miscellaneous remarks. It was, of course, impossible to secure all of this information in the three collected reports above mentioned, and even many of the single reports were deficient—an evidence of the inability of the average medical writer to give complete statements on even the simplest subjects. Obviously, too, the results obtained are much more reliable in some particulars than in others. Thus the evidence on such concrete simple items as age, sex, chamber ruptured and so forth can hardly be incorrect and in such large numbers must represent closely the true picture. Other details where the author's judgment is concerned, however, such as "survival after rupture" and "underlying cause," must be taken with greater reserve.

Before considering the results of the statistical study some details of our own 13 cases, which are fairly representative of various types, will be given.†

Case Reports. Our own series of cases can be divided into the following five categories: (1) Coronary sclerosis and thrombosis with myocardial fibrosis and necrosis, 9 cases; (2) coronary sclerosis and thrombosis with myocardial fibrosis only, 2 cases; (3) coronary sclerosis only with myocardial fibrosis and necrosis, 5 cases; (4) coronary sclerosis only with myocardial fibrosis, 2 cases; (5) no evidence about the condition of the coronaries, 4 cases.

Group I. Coronary Sclerosis and Thrombosis with Myocardial Fibrosis and Necrosis. CASE I.—W. L., a senile dement, aged seventy-nine years, was admitted to the Psychopathic Department of the Philadelphia Gen-

* References to these cases are too numerous to be included here, but will be furnished by the authors on request.

† It has not been possible to copy the exact words of the autopsy reports in all cases. The authors' therefore assume responsibility for the statements made.

eral Hospital, November 7, 1923, on the service of Dr. Rhein. No history of heart disease was obtained, though his feet were edematous, his heart sounds weak and peripheral vessels sclerotic. No murmurs, arrhythmia or cardiac enlargement were found. Urine and blood Wassermann tests were negative and the blood urea was 19 mg. The blood pressure was not taken. His condition continued unchanged until 1.30 A.M. of November 24, when he was found dead in bed, without the patients in the next beds having noticed anything unusual. Thirty minutes earlier he had talked normally with the night nurse.

At autopsy (P. G. H., 8236) I found the pericardial sac bulging with fluid and clotted blood (totaling over 350 cc.), which was found to be due to a small jagged opening, about 6 mm. long, in the posterior surface of the left ventricle, and slightly nearer the apex than the base. This did not at first admit a probe without danger of causing an artefact, but after the heart was opened it was found to connect diagonally with a similar opening in the endocardium near the posterior papillary muscle of the mitral valve and to admit easily a small probe. At neither point was there any clot. The heart weighed 400 gm. and measured 12 by 9 by 7 cm. It showed a thick, fatty, epicardial layer, with prominent and tortuous coronary arteries and mottled myocardium; toward the apex this almost resembled the scar tissue of a healed infarct. The muscle was flabby, but not tough. There were no pericardial adhesions. The right ventricle was apparently normal, its wall averaged 4 mm. in thickness and it contained a small amount of mixed red and white clot. The mural endocardium of the left ventricle was especially thickened at the lower end of the septum, and the myocardial wall was thinner at this point (6 to 8 mm.). The myocardium elsewhere measured from 10 to 14 mm. in thickness and showed no noteworthy fibrosis except in the area mentioned. The tips of the papillary muscles and chordæ tendineæ were very slightly thickened. The mitral and aortic valves were slightly thickened. The valve orifices measured: Mitral, 10, aortic, $7\frac{1}{2}$, tricuspid, 10, pulmonary, 7 cm. The orifices of the coronary arteries were somewhat sclerosed, especially the left. The right coronary artery, about 2 cm. from the orifice, was occluded with a dark red adherent clot, extending into the two branches for several centimeters.

Anatomical Diagnosis. Hemopericardium. Acute infarct of myocardium with rupture following coronary thrombosis. Myocardial degeneration with cardiectasis due to coronary sclerosis.

Other items of interest in the autopsy were a markedly atheromatous and fragile aorta, a phlebolith in the splenic vein, chronic splenitis and mixed nephritis, cerebral arteriosclerosis, thrombotic softening and convolitional atrophy.

Histology. Heart: Left ventricle: The subpericardial fibers are best preserved, though even here they are cloudy and swollen with indefinite striæ. There is some fragmentation and pigmentation, the nuclei are found to be large and rectangular. Deeper, these phenomena are more prominent and interstitial fibrosis appears, with much distortion of muscle fibers, several areas of fibrosis, containing but few muscle remnants, fill whole low-power fields. Fibrosis is most marked about the vessels. Serial sections through the ruptured area of the ventricle show a complicated picture of muscle degeneration, anemic infarction and, at a distance from the rupture, a separate, partly organized infarct. The jagged, oblique sinuous line of rupture can easily be traced through a definitely necrotic space, in an irregularly flat pyramid with the apex almost at the pericardium. The fibers are traversed in their long axis near the endocardial surface by the rupture, but transversely through a narrow subpericardial band.

The path of the rupture is lined by the bare fibers in some places, in others by a smooth composite of necrotic and interstitial tissue and infiltrated cells of various kinds. No thrombi are present. The tissue in which the rupture lies presents in a more marked degree the same lesions as more distant areas, but so close to one another that a continuous line of lessened resistance resulted. At some points, reaching almost to the line of rupture, the muscle is merely swollen and wavy, with more or less loss of striæ and tendency to pyknosis of muscle nuclei. There is considerable perinuclear pigment and some hyaline and fatty degeneration. At other places there has been marked complete loss of muscle fibers, giving a lacework appearance to the interstitial tissue, and this may be with or without cellular infiltration. Many areas have a dirty, slate-blue appearance (with hematoxylin and eosin), due to infiltrated polymorphonuclears, macrophages, some erythrocytes, etc., and much nuclear debris. These areas may be fairly massive or insinuated between the muscle fibers. A few zones, distant from the rupture, show beginning organization (numerous fibroblasts and capillaries, and pigment-laden macrophages). Peripheral zones of hyperemia are conspicuous by their absence. Still rarer are the areas of true anemic necrosis, that is, where the outline of the muscle fibers is preserved, but all structural detail and nuclei are lost. The same picture of marked perivascular fibrosis is present here, as in the other parts of the myocardium. Right ventricle: There are some changes in muscle fibers, but less marked. There is no marked fibrosis, though loose fibrous tissue and fat occur between the fibers.

Histologic Diagnosis. Coronary sclerosis and thrombosis, anemic infarct of myocardium; chronic interstitial myocarditis (perivascular). Organizing infarct.

Comment. The interesting features in this case are that rupture occurred during sleep, when there should have been the least amount of strain on the heart wall, and that it occurred in an unusual position, where the obvious chronic lesions were less advanced, but where the acute lesions were fraught with much greater danger, though not detectable by the naked eye. Although the myocardium grossly appeared the same as in many other localities, the microscopic picture clearly shows that following the recent coronary thrombosis (of at most a few days' duration), an anemic necrosis occurred, which offered less resistance than the more chronically injured tissue. From the obliquity of the tear it must have been, more or less, closed during systole, but allowed the blood gradually to escape during diastole until it so filled the pericardial cavity that the action of the heart was stopped. In regard to the supposed freedom from strain during sleep, MacWilliams has recently offered some interesting data which will be discussed later.

CASE II.—M. McB., aged about seventy years, a helper in the kitchen of this hospital, while at his usual work of peeling potatoes, complained of feeling badly, with a pain over his heart (May 26, 1924). A few minutes later he vomited and fell forward in his chair unconscious. His face became very blue, and his breathing stertorous. An intern who made a hasty examination could not hear his heart sounds at this time, and his lungs soon became filled with the coarse bubbling rales of pulmonary edema. He died less than five minutes after reaching the medical ward (Dr. Musser) and probably about fifteen minutes after his acute symptoms developed. Though elderly and rather feeble, previous to this he was not known to have been in poor health in any way.

Autopsy. (P. G. H., 8853, Dr. Eiman.) The pericardium extended 5 cm. to the right of the midline and practically to the ribs on the left. It contained 420 cc. of blood (partly in the form of currant-jelly clot).

The heart weighed 395 gm., measures 14.5 by 10 by 5.5 cm. and was of a peculiar, blunt, quadrangular shape. There were excessive amounts of pericardial fat, especially on the right side, the auricles were dilated, the ventricles contracted. A jagged, irregular tear, 7 mm. long, was found 3.4 cm. above the tip and 4.5 cm. to the left of the anterior coronary artery (that is, near the left border). The probe passed through this tear without any resistance into the left ventricle, where it was found to have traversed the split base of one of the mitral's papillary muscles. The myocardial wall, which here measured 11 mm. in thickness was mottled brownish-red, with areas of brighter red and small irregular streaks of a tarry substance were found in their centers. The myocardium elsewhere was cloudy and brown in color. Its walls varied in thickness from 5 mm. at the tip of the left ventricle to 20 mm. in its thickest portion, the right ventricle was 5 mm. thick. The valve leaflets showed no noteworthy lesions; they measured as follows: Mitral, 9.3 cm.; aortic, 6.3 cm.; pulmonic, 7.5 cm.; tricuspid, 12.3 cm. The coronary arteries were greatly fibrosed and calcified; the anterior descending branch just above the site of the rupture had practically no lumen left, and was completely filled with red clot.

Anatomical Diagnosis. Hemopericardium. Acute suppurative myocarditis with rupture. Marked coronary sclerosis and thrombosis (?) of anterior descending branch. The other lesions noted were chronic fibrous changes in the pleura, spleen, kidney, pancreas and aorta, and a small right testicle with absence of left testicle and feminine body proportions and hair distribution.

Histology. Heart: Immediately beneath the normal epicardium and thick fatty layer the fibers (cut in cross section) have a relatively normal appearance, except that in some areas there is considerable replacement with fibrous tissue. About 2 mm. deep there is a grossly visible blue staining zone, due to the occurrence of polymorphonuclear leukocytes and tissue debris, packed between the muscle fibers and grouped in circular areas. No bacteria can be found, even with special stains. The fibers here are narrowed by compression and either partly or wholly necrotic. For the remaining depth of the section (that is, as far as the endocardium), the muscle fibers, though not compressed, are wholly or partly necrotic, and frequently surrounded by clumps of detritus and leukocytes. The Purkinje fibers are excessively prominent, swollen and apparently necrotic.

Histologic Diagnosis. Acute infarct with liquefaction necrosis, due to coronary thrombosis.

Comment. The clinical history of this case is rather typical and illustrates some of the difficulties of proper study. Differential diagnosis from fatal coronary thrombosis would have been impossible. The absence of any known previous illness, especially in view of the lesions found, is noteworthy, though not infrequent.

The gross and microscopic signs of acute inflammation suggest that the heart may have been predisposed to rupture by bacterial suppuration; but in the absence of demonstrated bacteria and the presence of coronary thrombosis, it seems more probable that the necrotic infarct had liquefied and that the leukocytes were attracted by the sterile process.

CASE III.—M. F., an obese Irishwoman, aged fifty-seven years, was admitted to the nervous department of this hospital on Dr. Pemberton's service on August 14, 1902, with the diagnosis of left-sided hemiplegia. There was nothing noteworthy elicited in her family and past history. Her present illness had come on during sleep, four weeks before, with inability to use her left arm and leg, but without speech disturbance. This condition had persisted without much improvement. Her pulse was rapid and sclerotic; there were no cardiac murmurs. Her urine was nega-

tive. On January 31, 1905, she went to bed feeling as usual. During the night the nurse noted that she had become cyanotic and that her breathing was stertorous and a few moments later she died.

Autopsy. (P. G. H., 440, Dr. Funk, twenty hours postmortem.) The pericardium contained a considerable amount of fluid and clotted blood. The heart was relatively small, weighing 350 gm. with a heavy layer of subpericardial fat. On the posterior surface of the left ventricle, 3 cm. above the apex, was a laceration, 15 mm. long and 5 mm. wide, parallel to the long axis of the heart. Near the rupture were numerous hemorrhages in the pericardial fat and a soft greasy yellow-pink area which occupied almost half the ventricle. The line of rupture was jagged and tortuous, reaching the endocardium just posterior to the base of the anterior papillary muscle. There was no evidence of scar tissue formation. The coronary arteries were markedly sclerosed. The lumen of the right coronary was especially diminished and contained clotted blood, which was probably an antemortem thrombus.

Anatomical Diagnosis. Hemopericardium. Rupture of posterior wall of the left ventricle, due to acute infarction (?) following coronary thrombosis. (At the time of autopsy this was termed local fatty degeneration.) There was also found cirrhosis of the liver and chronic parenchymatous nephritis.

Histology. Sections were not taken at the time of autopsy, but nineteen years later when the heart was first opened. Section of the posterior descending branch confirms the marked sclerosis with great narrowing of the lumen. Smaller branches near the rupture are totally occluded with dense fibrous tissue. The muscle adjacent to the line of rupture is much fragmented, and shrunken or wavy and disintegrated with loss of striæ and nuclei. The areas of necrosis are not extensive, however. There is no cellular infiltration, except for clumps of erythrocytes in the epicardial fat, and there is only a slight layer of fibrin almost free from cells. The muscle cells immediately adjacent to the line of rupture contain much golden pigment (hemosiderin?). There is considerable periarterial fibrosis.

Histologic Diagnosis. Coronary sclerosis and fibrous occlusion. Myocardial fibrosis with areas of necrosis.

Comment. This presents the usual clinical history and pathologic picture of coronary disease with myocardial degeneration, followed by thrombosis of a branch with infarction of the stricken area, and in turn by spontaneous rupture.

CASE IV.—M. K., an obese nervous white woman, aged fifty-eight years, was admitted to Dr. Burn's service of the neurological department of this hospital on August 27, 1923, with a diagnosis of right-sided hemiplegia. She complained of "nerves," and said she had had "neuritis" of her left arm and leg for two years. She denied any past illnesses, had had five children, two miscarriages and had a negative Wassermann reaction.

Physical examination showed the usual signs of an old hemiplegia, with equal pupils, partial aphasia and paralysis, and emotional instability. The heart dulness was slightly increased with a faint, apical, systolic murmur, not transmitted, and weak distant sounds. The urine showed a trace of albumin, but no casts and the blood chemistry was negative.

Except for persistent constipation, the patient continued the same for eight months, without any signs of cardiac decompensation. Suddenly at 1 A.M., while lying in bed, she became pulseless, very cyanotic and dyspneic, and died within fifteen minutes. When seen by the intern she was unconscious, though only fifteen minutes before the attack she was complaining merely of weakness and was somewhat dyspneic.

Autopsy. (P. G. H., 8772, Dr. Lucke, twelve hours after death.) The pericardial sac was distended with about 300 cc. of frothy clotted blood. The heart was of normal shape and somewhat enlarged, weighing 520 gm., and measuring 14 by 11 cm. There was much epicardial fat, varying from 4 mm. at the left apex to 8 mm. in thickness at the left base. Just above the tip of the right ventricle there was a slight bulging of the epicardium, due to a diffuse irregular hemorrhagic infiltration, roughly 4 cm. in diameter. Section here showed the epicardial fat to be 6 mm. thick over a thin strip of muscle, which varied from 1 to 2 mm. in thickness. In many places the fat extended into the left ventricular wall, especially in the bulging hemorrhagic area, where there was an irregular tear, 2 cm. in diameter, communicating with the right ventricle. The neighboring tissue was densely infiltrated with blood. The left ventricular wall averaged 23 mm. in thickness, but here thinned out to 6 mm. A walnut-sized thrombus adhered to the left apex. The chordæ tendineæ and papillary muscles were normal; the mural endocardium slightly thickened, especially below the aortic ring. The aortic leaflets had slightly stiffened, atheromatous bases, the valves otherwise being normal and measuring: Aortic, 8; mitral, 10, tricuspid, 12.5, pulmonary, 8.2 cm. The coronaries were somewhat tortuous and had an irregularly thickened intima. In the right coronary (the walls of which were much more diseased than the left and were thick, distorted and crumbling), a firm red clot filled the lumen, beginning about 2 cm. from its origin. Both descending and horizontal branches contained the same kind of clot as far as could be traced. It was not possible to ascertain the primary site of thrombus formation. A branch from the main artery (given off before the main descending branch) was pointing straight for the rupture. This also was filled with red clot, but became too small to trace grossly before the rupture was reached. The muscle in this area did not vary grossly from the myocardium elsewhere.

Anatomical Diagnosis. Hemopericardium. Rupture of right ventricle. Coronary sclerosis with thrombosis of right branch. Hemorrhagic infiltration of apex with thinning of walls of both chambers. Antemortem clot in apex of left ventricle.

Histology. Large areas of fibrin, erythrocytes and cellular debris merge inextricably with muscle fibers in various stages of distortion and degeneration. In the less changed areas the muscle fibers are compressed between hemorrhagic infiltrates and numerous polymorphonuclears. There is marked evidence of scavenging and new tissue formation with many phagocytes, plasma cells, eosinophils and beautiful "polyblasts," with relatively few new bloodvessels. The larger branches of the coronaries are much sclerosed and distorted and many filled with antemortem clot.

Histologic Diagnosis. Coronary sclerosis and thrombosis. Extensive necrosis of myocardium with beginning repair.

Comment. The rupture of the right ventricle accords with the thrombosis of the right branch. The extension of the necrosis into the left apex indicates that in this case the posterior descendens supplied more than its usual amount of myocardium. Correlation of clinical and pathological evidence shows that the coronary thrombosis (which from the histological picture must have occurred at least many hours before death) gave no signs or symptoms and that the terminal symptoms followed the actual rupture of the ventricular wall.

CASE V.—A man, aged thirty-eight years, of dissolute habits, during a drunken debauch at Atlantic City fell heavily against a box for mixing mortar, hitting the edge against his precordial area. When seen by Dr. Henry Marvel, several days later, he had considerable precordial pain,

but no diagnosis was made. No further details are now available except that death occurred suddenly. .

Autopsy. (U. of P. Dept. of Pathology, No. 345.) The pericardial cavity was filled with clots of blood. About half way up the outer wall of the left ventricle in the visceral pericardium was a transverse tear, 3 cm. in length, which extended into the myocardium for about two-thirds of its depth. No mention is made of the coronaries grossly, but histologically the arterioles were reported as occluded and the myocardium near the rupture as acutely necrotic. (As Dr. Marvel's records were not available, the autopsy notes, supplemented by verbal statements of Dr. A. J. Smith, have been used with his kind permission.)

Comment. It is more probable that trauma played a prominent part in this case, but that it acted by injuring the coronary with subsequent thrombosis formation and that rupture occurred "spontaneously" as a result of the thrombosis.

CASE VI.—A housekeeper, female, aged sixty-five years, entered the Peter Bent Brigham Hospital at 9 A.M., and died suddenly at 5 P.M. She had had dyspnea for ten years and for more than a year had many attacks of sharp precordial pain, most apt to come on during excitement. Her chief complaint was of pain over the heart and in the stomach; she has had pneumonia but no rheumatic fever.

Autopsy. (P. B. B., No. 1744.) The pericardial cavity contained a dark purple clot which surrounded the heart like a cast. On removing this a small rupture of the left ventricle was found situated just to the left of the septum anteriorly, about 4 cm. below the base. This area of rupture measured about 1 cm. in length, was red and the margins fragmented. On the left side of the heart were numerous, rather fresh, friable mural thrombi situated over the lower half of the septum and apex, about the area of rupture. From the ventricular side this area of rupture gave the impression of a punched-out brick, which admitted the tip of the little finger halfway through the musculature of the heart. There were yellow and rather pale mottlings of the myocardium in this region, more suggestive of fat than of actual necrosis. There was no obstruction or narrowing of the orifices of the coronary arteries. On opening the anterior coronary artery which fed the area in which the rupture occurred there were several mural thrombi found on the intimal surface, the first being about 2 cm. beyond the orifice. Some of these were firmly adherent, paler and apparently considerably organized.

Anatomical Diagnosis. Coronary thrombosis. Rupture of myocardium of the left ventricle. Hemopericardium.

Histology. In certain areas the vessels are markedly congested and are surrounded by masses of blood. In these areas the muscle fibers are necrosed, and have among them a moderate polymorphonuclear exudate. This is apparently about the point of rupture. Numbers of small clumps of bacteria (pyknotic nuclei ?*) are also present here. The muscle fibers in other areas show a moderate degree of fragmentation.

Comment. The cause of rupture was evidently due to acute massive necrosis of myocardium caused by either embolus or thrombus.

CASE VII.—A man, aged seventy-one years, the owner of a general store, entered the hospital complaining of pain in the epigastrium, of six weeks' duration. The pain radiated to the chest, usually lasted about three minutes and was sometimes relieved by rest. It bore no relation to meals. He had vomited three times. The last attack, which began on the morning of admission, began in the epigastrium and radiated to chest, right shoulder

and arm. About two hours after physical examination the nurse found him gasping for breath and he stopped breathing shortly after.

Autopsy. (P. B. B., No. 19101.) The pericardial cavity contained 350 cc. of bloody fluid. About the auricle, posteriorly, were large masses of clotted blood. The heart weighed 430 gm. On the anterior surface of the left ventricle, about 2.5 cm. from the apex and running downward and to the left, was an oblique linear rupture of the pericardium and myocardium just at the left of the interventricular septum, but visible on the endocardial surface, as only 1 cm. in length. The softened area about this rupture was supplied by the descending branch of the left coronary artery. About 2.5 cm. above the softened and discolored portions of the left ventricle this vessel was occluded by an atheromatous plaque which had become ulcerated with formation at that point of a dark red thrombus, about 4 mm. in length. No thrombi were demonstrable in other coronaries. The myocardium of the left ventricle in the softened area was found to be pale in several places, and particularly beneath the epicardium were several yellowish-white, irregularly shaped areas, from 2 to 8 mm. in size, suggesting anemic infarcts.

Anatomical Diagnosis. Infarction of the left ventricle with rupture and hemopericardium; thrombosis of descending branch of left coronary artery.

Histology. The cardiac muscle is degenerated and fragmented. At places it shows marked hyaline degeneration with infiltration of few leukocytes and fat globules.

Comment. None.

CASE VIII.—A housekeeper, female, aged seventy-four years, on her first admission, which occurred a year previously, was discharged with a diagnosis of lobar pneumonia, thrombophlebitis and hypertension. She entered this time with a complaint of dyspnea. She had had two or three marked attacks of severe dyspnea and vertigo during the past year. On the day before entrance she was found sitting in a chair in an aphasic condition. A short time later a sharp pain was noted over the precordium. While in the hospital she suddenly began to cough, and died.

Autopsy. (P. B. B., No. 2164.) The pericardial cavity contained 150 cc. of bright red fluid and a large amount of blood clot. The heart weighed 410 gm. Over the anterior surface of the left ventricle and a portion of the right ventricle there was a reddish, granular exudate over an area about 5 cm. across, which was darker than the rest and surrounded a rent in the visceral pericardium which measured 3 cm. in length. This rent began 2 cm. below the pulmonary valve, and extended downward in a vertical direction. Upon making coronal sections a diffuse hemorrhage beneath the pericardium was found surrounding the opening. More coronal sections 3 cm. apart showed this rent to be an irregular slitlike opening, extending outward from the myocardium. It was located in the upper portion of the left ventricle in the tract of the anterior descending branch of the left coronary artery. The total area involved part of the anterior wall of the left ventricle and a portion of the septum downward to within 5 cm. of the apex. A small conical thrombus was found about 2 cm. below the origin of the anterior descending branch of the right coronary. In the wall of the left ventricle there was a large, adherent, friable mural thrombus.

Anatomical Diagnosis. Ruptured infarct of left ventricle. Thrombosis of anterior descending branches of the left coronary artery. Hemopericardium.

Histology. "The picture is that of necrosis superimposed on a myocardium with many cicatrices. There is very marked destruction of

muscle in places with accumulations of polymorphonuclears and débris that give the appearance of abscess formation."

Comment. A typical case, with an interesting association with a probable cerebral thrombosis shortly before.

CASE IX.—A man, aged sixty-three years, the superintendent of a dry-goods store, one year ago noticed that he occasionally was able to hear his heart beating somewhat irregularly. These attacks came on after excessive irritating and nervous work, and there was no associated dyspnea. He tired more easily than usual. He never noticed swelling in the feet or pain in the chest or other symptoms. Two weeks before admission the patient underwent some unusual strenuous exercise and the following day at 10.30 he suddenly felt a sensation of heaviness in the chest, unassociated with palpitation or dyspnea. It gradually became worse, and the patient was forced to pace about in agony, being unable to lie down. After continued pain in the chest and one very bad attack, he was admitted to the hospital, and died suddenly in the morning when raising himself in bed, after spending a comfortable night.

Autopsy. (P. B. B., No. 22100.) About 750 cc. of blood and blood clot was found in the pericardial cavity. Several light reddish-gray, somewhat friable clots, probably antemortem, were also present. There was a rent in the heart muscle on the anterior surface about 3 cm. from the left border of the heart and 8 cm. from the apex. The apex of the heart was soft and discolored. The heart, plus the clot, weighed 800 gm. (net, 700 gm.). The left ventricle was markedly dilated and had an aneurysmal dilatation at the apex, about 6 cm. in diameter. This dilatation was filled with a pinkish-red, granular, friable clot, evidently antemortem. The wall was extremely thin at this area, measuring 5 mm. in thickness. The thinning of the left ventricle began on the posterior wall, just below the attachment of the posterior papillary muscle. The intraventricular septum was apparently not involved. The left coronary artery had an arteriosclerotic lesion on the anterior surface of the heart about 1.3 cm. from its origin. At this portion there was a small pinkish-gray clot, about 1 mm. in diameter, probably a thrombus. The descending branch of the same artery was completely sclerosed a short distance from its origin. The right coronary was apparently normal.

Anatomical Diagnosis. Aneurysm of apex of the heart with mural thrombus. Rupture of the heart. Infarct of the heart. Hemopericardium. Obliteration of left descending coronary artery.

Histology. Some sections taken through the aneurysmal dilatation show extreme infarction of heart muscle, in which the entire musculature has been converted into a structureless débris, eosin staining, and in which are scattered nuclear fragments and an occasional polymorphonuclear leukocyte. In a section showing infarct and adjacent heart muscle, the fibers are pale, the nuclei are fragmented and some of the bundles of muscle fibers are necrotic and converted into a granular acid-staining débris. Between the muscle bundles is an increased amount of connective tissue. Young fibroblasts are seen in some areas. Dense scar tissue is also present.

Comment. This case offers an interesting correlation of clinical and pathological findings. Although the aneurysmal dilatation was infarcted, the actual rupture occurred slightly higher up.

Group II. Coronary Sclerosis and Thrombosis with Myocardial Fibrosis Only. **CASE X.**—G. S., a busy surgeon, aged sixty-two years, of good habits and health, complained for several days of pain in his upper abdomen, but it was not sufficient to stop him in his active practice. He had a good past history, except that he had been known to have a moderate

amount of arteriosclerosis with hypertension for several years. He neither smoked nor drank. The morning of his death his discomfort was sufficient to keep him in the house, and soon developed into a "terrible oppression" in his chest, together with extreme restlessness, which persisted in spite of liberal doses of morphin hypodermically. This continued for about four hours, when he gasped and suddenly died.

Autopsy. (Presbyterian Hospital, No. 2, 1922, Dr. Eiman, after embalming.) The pericardial cavity was found distended to its utmost capacity with dark red soft clotted blood. The heart weighed 420 gm., was rather pointed and contracted and measured 14 by 8.5 by 6.8 cm., and showed considerable subepicardial fat. On the lower anterior surface of the left ventricle, 3.5 cm. above the tip, was an irregular hemorrhagic area, 3 by 2.5 cm., in the center of which was a jagged rent, less than 1 cm. in length. A probe was passed without resistance into the left ventricle. On opening the left ventricle, at the angle of the septum and the anterior wall near the apex, there was found a soft, partly organized mural thrombus, measuring 6.5 by 2.3 by 1.8 cm. The portion of the wall to which the thrombus was attached was slightly bulging and concave. The inner aspect of the rupture was hidden in the mural trabeculae, near the attachment of the thrombus, but was found to be smaller than the outer. The left ventricle was 5 mm. thick at the aneurysm, and 20 mm. at the base; the right ventricle, 7 mm.; the auricles, 1 to 2 mm. The myocardium was toughened and discolored by the embalming, but was firm and apparently normal. Even the thinner portion still had considerable muscle tissue left. The pulmonic valves were normal; the others slightly thickened.

The left coronary artery divided anomalously less than 1 cm. from its origin. The branches, which were almost parallel for several centimeters were uniformly thickened and considerably calcified, but with ample lumina. Where the descending branch passed over the elevation of the base of the left ventricle its lumen suddenly narrowed to about 1 mm. in diameter and from there on was filled with a firm dark clot, which extended into the branch that supplied the ruptured area. This thrombosis probably occurred shortly before death. No thrombus was found in the right coronary. The valves showed no noteworthy lesions except for slight thickening along the edges of the mitrals, the bases of the aortic leaflets and diffusely in the tricuspid.

Anatomical Diagnosis. Hemopericardium. Rupture of left ventricle following thrombosis of the descending branch of the left coronary. Beginning apical cardiac aneurysm. Anomalous left coronary artery.

Histology. Muscular elements are surprisingly well preserved in sections from all chambers. The amount of perivascular fibrosis is moderate, about the same in all chambers and about what would be expected at sixty-two years. It is slightly greater in amount near the rupture. There is some perinuclear pigmentation. The main coronary branches show a disproportionate amount of sclerosis (more than the renal and much more than the aorta). Some lumina are filled with antemortem clot. Section from the edge of the rupture shows considerable hemorrhagic and some leukocytic infiltration but no evidence of necrosis. No ruptured fibers are seen in the section, and at this level the opening was caused by separation rather than rupture of the fibers. Section from the bulging thinned area shows pressure atrophy of the fibers, but surprisingly little degeneration and fibrosis.

Histologic Diagnosis. Marked coronary sclerosis and recent thrombosis. Perivascular fibrosis of myocardium. Pressure atrophy at dilated area and hemorrhagic infiltration.

Comment. In this case, in spite of the relatively small amount of perivascular fibrosis found microscopically, coronary disease was undoubtedly

a factor in the beginning of cardiac aneurysm. The coronary thrombosis, though it was too recent to show any signs of organization, or even to cause visible changes in the myocardium, was apparently a factor in further weakening the myocardium to the point of rupture. The course of the anomalous coronary apparently predisposed it to sclerosis; what further influence the anomaly may have had is not determinable.

CASE XI.—A housewife, aged sixty-one years, was admitted to the hospital, December 23, 1924, because she had been "out of her head" for the past twenty-four hours. History given by her husband: Mother died of diabetes, aged seventy-eight years; one sister had diabetes. Her past history was negative prior to the present illness, except for impaired hearing in the left ear in the last three years, associated with some earache and buzzing in that ear. Her present illness began two years ago with loss of weight (from 160 to 130 pounds in six months), increasing weakness, great thirst and hunger. Sugar was found in the urine. Her appetite was excessive and there was marked polydipsia. Three days before admission the patient became so weak that she went to bed. The second day before admission she became unconscious and the respirations labored. In the first nine hours following admission the patient received 120 units of insulin with some cereal and milk. The patient then seemed much better and was breathing quietly. She had a good night and in the morning seemed much improved. At 7.10 A.M., without any warning, or noticeable distress, the patient died.

Autopsy. (P. B. B., No. 24100.) The pericardial cavity contained a large amount of blood clot, weighing 115 gm. The heart was distinctly enlarged and weighed 340 gm. On the posterior surface of the left ventricle, just to the left of the intraventricular septum, an irregular yellowish-white area of scar tissue was seen, 2 cm. in greatest dimension. In the center of this area was a slitlike opening in the heart wall, 4 mm. in length, with ragged edges. The heart wall surrounding the opening was represented by a layer of fibrous tissue about 2 mm. in thickness. On viewing the heart wall from within, a definite hole was seen in the myocardium, with ragged, necrotic edges, large enough to admit the tip of the finger. The right coronary artery at a point 3 cm. from its origin was occluded by a definite thrombus 8 mm. in length and grayish-red in color. This thrombus was evidently of recent origin. The artery was found to lead into the area of infarction described above, where its lumen was lost. The left coronary was negative.

Anatomical Diagnosis. Infarction of heart. Rupture of left ventricle at site of infarction. Thrombosis in right coronary artery (recent). Hemopericardium.

Comment. Another typical case associated with a cerebral lesion.

Group III. Coronary Sclerosis Only with Myocardial Fibrosis and Necrosis.

CASE XII.—W. M., a man, aged seventy-four years, was admitted to the service of Dr. Riesman, in this hospital, October 16, 1911, with signs of heart failure. The brief history showed that he was a hard drinker and had had most of the contagious diseases but denied venereal disease. He soon developed severe precordial pain, acute dyspnea and cardiac arrhythmia, which progressed to true angina pectoris, Cheyne-Stokes respiration and death on the fourth day after admission.

Autopsy. (P. G. H., 2852, Dr. Ellis, eleven hours after death.) Autopsy showed 1100 cc. of blood in the pericardial cavity. The heart was fairly large, weighing 570 gm., with a moderate amount of epicardial fat. On the anterior surface of the left ventricle near the septum, and 2 cm. from the apex, was a slightly angular tear, 7 mm. long, roughly parallel with



FIG. 1.—Case I showing rupture on posterior surface of left ventricle and surrounding pericarditis. The thrombosis of the descending coronary cannot be detected.



FIG. 2.—Case I showing oblique direction of tear with endocardial opening hidden behind the papillary muscle.

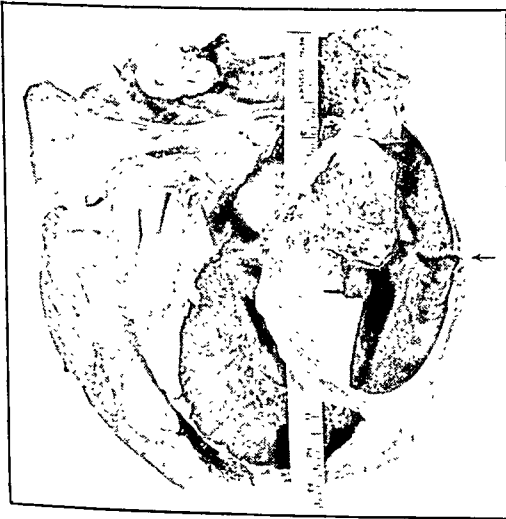


FIG. 3.—Case II with arrow pointing to line of rupture through wall of ventricle. Subepicardial hemorrhage is also shown.



FIG. 4.—Case III, the ragged tear is seen joining the lower area from which section was taken.



FIG. 5.—Case IV showing hemorrhagic infiltration and thinning of apex. Edge of the rupture is best seen in the tip of the reflected portion.



FIG. 6.—Case V showing transverse ragged tear 3 cm. in length, not penetrating into the cavity. Section has been taken in the middle of its upper border.

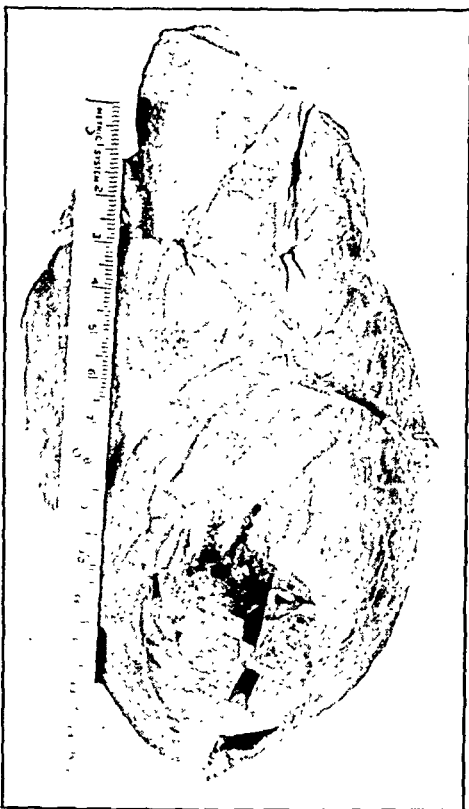


FIG. 7.—Case X showing the bulging hemorrhagic zone in left ventricle, from which various sections have been taken.



FIG. 8.—Case X, interior of left ventricle showing mural thrombus, subendocardial hemorrhage and great thinning of wall.



FIG. 9.—Case XII showing large, irregular
“blow out” type of rupture.

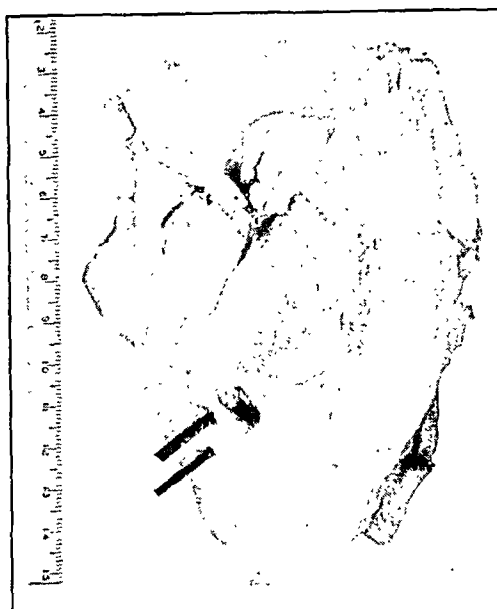


FIG. 10.—Case XVIII showing double rupture
(with rods inserted) also place where section is
taken. This specimen was fifty (50) years old at
the time it was photographed.

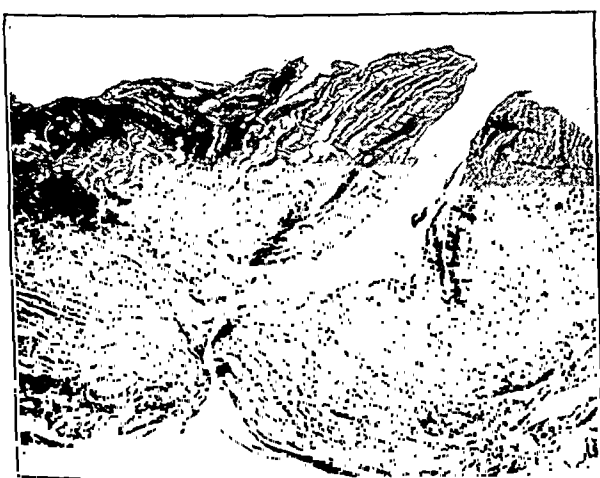


FIG. 11.—Photomicrograph of line of rupture
of Case I.

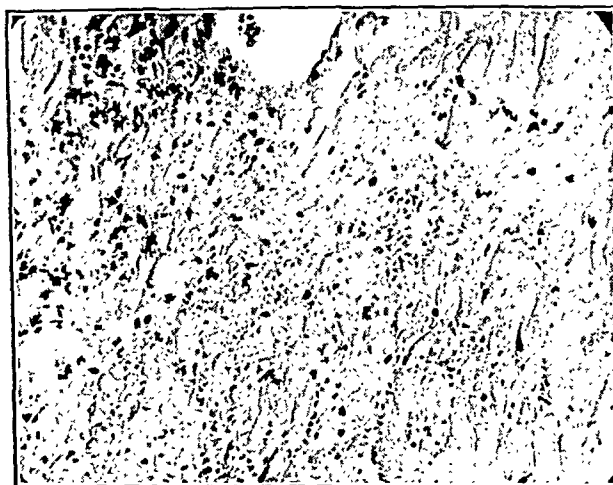


FIG. 12.—Photomicrograph of anemic infarct,
following coronary thrombosis, with infiltration
of red blood cells in the center of the picture and
leukocytes at one edge. Case I.

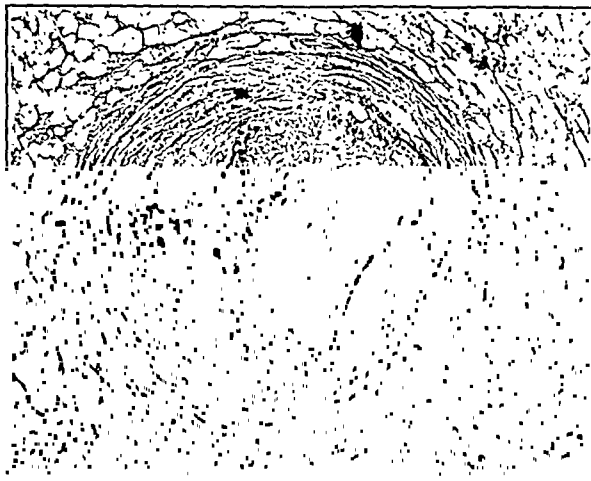


FIG. 13.—Photomicrograph of occluded branch of coronary artery. Case III.

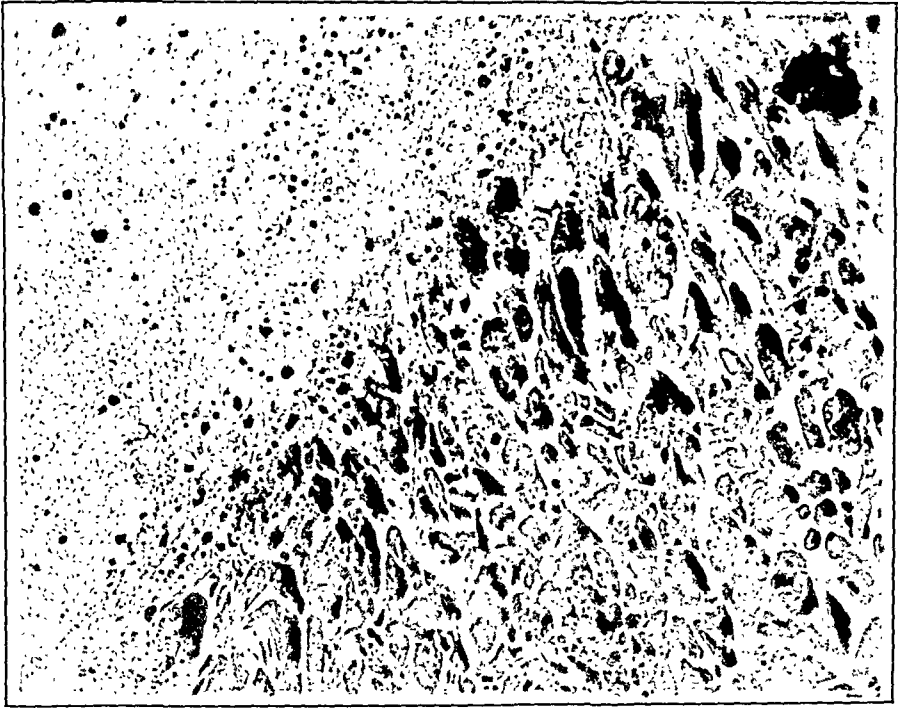


FIG. 14.—Photomicrograph of edge of rupture of Case III, showing hemosiderin granules in muscle cells along edge.



FIG. 15.—Photomicrograph of Case IV showing cellular infiltration in myocardium and epicardial fat and polyblastic connective tissue formation.

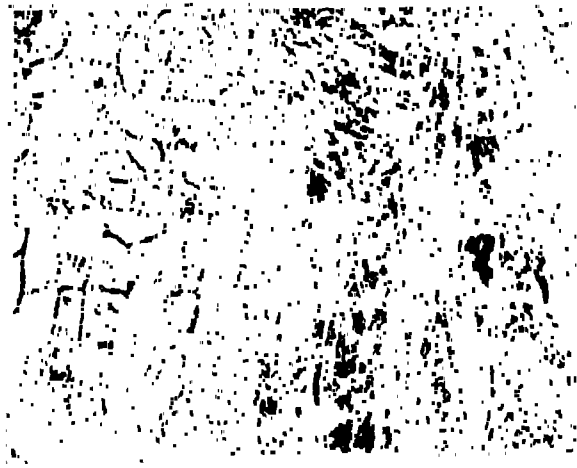


FIG. 16.—Photomicrograph of extensive myocardial fibrosis, Case XVIII.

the descending branch, with ragged edges discolored brown. Clotted blood was adherent and the muscle was friable. The wall of the left ventricle, which at the base was 2.3 cm. thick, measured 0.6 cm. at the apex, being thinned "almost to a membrane," and the cavity was dilated. It was a pale red color with yellowish spots especially toward the apex. Trabeculation was marked, though the muscle columns were flat and stretched. The tear was at the upper edge of the pouch and not at its thinnest point. The coronary arteries were sclerotic but the lumen was wide and partly filled with dark blood. No antemortem thrombus was found.

Anatomical Diagnosis. Hemopericardium. Rupture of left ventricle near dilated apex. Coronary sclerosis but no thrombosis.

Histology. There is a slight fleecy fibrosis between the fibers and, in patches, atrophy of muscle fibers with vacuolization and loss of longitudinal striæ. Areas of hemorrhage near the rupture vary with others of moderate round cell and polymorphonuclear infiltration. At the line of rupture the fibers are necrotic (wavy with total loss of nuclei and striæ). Many fibers terminate abruptly with ragged ends.

Histologic Diagnosis. Fibrosis and atrophy of myocardium. Necrosis and rupture of myocardium with hemorrhagic and cellular infiltration.

Comment. A good example of necrosis and rupture of the myocardium without coronary thrombosis. The coronary sclerosis was doubtless an important factor in the production both of the pouching and of the necrosis.

CASE XIII.—A man, aged seventy-four years, retired, complained of shortness of breath and said his stomach rebelled against certain foods. A minute after the doctor left him the patient died.

Autopsy. (P. B. B., No. 1541.) The pericardial cavity was full of blood clot, which entirely surrounded the heart. On the posterior side of the left ventricle was a raised area, 2 cm. in diameter, which was slightly bluish in spots and showed one slit, 13 mm. in length, through which a probe could be passed into the left ventricle. Above this was the appearance of a slit, 5 mm. in length, but there was no aperture. There was marked degeneration of the muscle of the ventricular wall, for a considerable distance on each side of the place of rupture. The coronary arteries showed a considerable degree of sclerosis and many places where the lumen was almost obliterated.

Anatomical Diagnosis. Rupture of left ventricle. Hemopericardium. Coronary sclerosis. Chronic myocarditis.

Histologic Diagnosis. Fatty degeneration. Necrosis and histolysis of the cardiac muscle.

Comment. Although the lumen of the coronary artery was not entirely obliterated, obstruction was sufficient to cause infarct and rupture.

CASE XIV.—A housewife, aged forty-two years, complained of pain in the back for two weeks. Her past history was negative. Four days before admission the pain radiated to the left arm. On the day before admission it was unusually sharp and lasted fifteen minutes. Physical examination showed a woman in much pain, rapid pulse and low blood pressure. She died after a week's stay in the hospital.

Autopsy. (P. B. B., No. 20104.) The pericardial cavity contained 250 cc. of bloody fluid and a large dark red blood clot almost surrounding the right auricle. Several clots were present in the apex region of the sac. The heart weighed 400 gm. On the anterior surface, in the wall of the left ventricle, was a rent, 3.5 cm. long, extending obliquely downward to the left, at the beginning about 1 cm. to the left of the anterior branch of the coronary artery. There was a thin delicate deposit of fibrin about this, surrounding it in a zone about 4 cm. in width. An incision in the

heart passing at right angles to this rent disclosed an actual defect in the wall as long as the linear lesion appearing on the surface, and about 4 mm. in width. There was here considerable loss of myocardial substance in the left ventricle, so that it was only 3 mm. in thickness in its greatest part. Filling this defect and about one-half of the ventricular space was a grayish-red thrombus, which had a relatively smooth surface. The remaining portion of the myocardium of the left ventricle measured 1.5 cm. in thickness, of a somewhat red cast with a few grayish-white lines, altogether suggesting fatty infiltration. The coronary arteries as a whole were markedly thickened, the right coronary showing great diminution of the lumen by calcification and atheromatous material concentrically arranged. Dissection of the left coronary showed much thickening of its wall along its entire length, and almost complete obliteration of the lumen of the main trunk. Histologically arteriosclerosis was rather generalized, but most marked in the artery where thrombosis occurred, with resulting infarction.

Anatomical Diagnosis. Rupture of the left ventricle of the heart, with thinning of its wall due to infarction. Hemopericardium. Thrombosis of the anterior descending branch of the left coronary artery.

Comment. Infarction due to the coronary sclerosis had probably existed for at least several days before the rupture occurred.

CASE XV.—A woman, aged sixty-three years, a practical nurse by occupation, had previously been at the hospital with diabetes and had frequent attacks of moderate dyspnea and palpitation with high blood pressure for many years. She came in the day before death, after having pain in the chest for six weeks, brought on by exertion. On the night before death she had severe pain beneath the sternum, radiating to the neck and shoulders.

Autopsy. (P. B. B., No. 21174.) The pericardial cavity contained 400 cc. of fluid which contained about 100 cc. of blood clot of recent formation. The fluid was thin and dark red. The heart weighed 400 gm. On the pericardial surface, about 4 cm. from the apex, in the region of the septum and the anterior descending branch of the left coronary artery, there was a slit about 3 cm. in length, through which blood oozed and around the margin of which there was discoloration for a distance of 8 mm. The slit was found to be 0.5 cm. from the septum and in the path of the above-mentioned coronary artery. There were also small adherent mural thrombi. This was undoubtedly the place of rupture and the coronary leading to this area was more contracted than the other coronaries and showed more sclerosis, the lumen being definitely smaller. No actual thrombi or emboli were found. The other coronaries were patent and distended.

Anatomical Diagnosis. Rupture of the heart with infarct of the left ventricle. Arteriosclerosis of the anterior branch of the left coronary artery. Hemopericardium.

Histology. Sections from the left ventricle show considerable areas of hemorrhage and blood clot in the myocardium. The muscle bundles are large and present several areas of scarring, also foci of fat between the muscle bundles. Many of the muscle fibers show parenchymatous degeneration. One of the sections shows in addition considerable numbers of polymorphonuclears and have infiltrated the myocardium. The appearance is that of acute and chronic myocarditis with rupture of heart.

Comment. Again sufficient coronary obstruction was present to cause infarction without actual obliteration. Duration of the infarct is problematical.

CASE XVI.—A man, aged seventy-two years, a cigar-maker, entered the hospital, February 26, 1925, complaining of pain in the chest. His family history was unimportant. For one year he had been troubled with nocturia, which had steadily become more annoying, so that for a few months he was forced to get up every half hour to urinate. For a few months he had complained of difficulty in starting urination, dribbling and burning micturition. Thirty-six years ago he had a chancre for which he received treatment with mercury, but subsequently a skin rash appeared which cleared on taking "black drops." In his present illness he had been dyspneic on slight exertion for several months. Occasionally he had been awakened at night with an attack of sharp substernal pain, which shot across the left side of his chest and down the ulnar surface of his left arm. These attacks occurred on exertion and sometimes made him feel an abnormal fear of death. Four days before entry, while sitting in a moving-picture house, he was seized with an attack much worse than any he had previously experienced. He went home and went to bed. The pain diminished considerably, but persisted in a milder degree until entry to the hospital. Except for frequency and dysuria, he was fairly comfortable until his fifth day in the hospital, when immediately after the use of a urinal he suddenly became pulseless, cyanotic and died almost immediately.

Autopsy. (P. B. B., No. 2537.) The pericardial cavity contained about 100 cc. of fluid blood as well as a large mass of blood clot lying between the two layers of pericardium. This clot weighed 420 gm. The heart was enlarged, weighing 500 gm., and was normal in shape. On the external surface and the posterior surface of the left ventricle, 1 cm. to the left of the intraventricular septum and about midway between the apex and the mitral valve, was a slitlike tear in the ventricular wall. This opening extended completely through the wall of the ventricle. On the external surface it was 2.5 cm. in length and 0.5 mm. in breadth, while on the inner surface it was about 1.5 cm. in length. The myocardium, radiating about the rupture for a distance of 2 to 3 cm., was mottled, deep red and reddish-gray, and here the tissue was apparently more friable than elsewhere in the ventricular wall. The gross appearance was that of infarction. The left coronary artery, from its point of origin down to its bifurcation, showed considerable arteriosclerotic thickening of its walls, and in some areas its walls were calcified. The anterior descending branch, at a point 1 cm. below its origin, had a very rigid calcified wall, and its lumen was so narrow that it barely admitted the sharp point of the scissors. The circumflex branch of the left coronary artery showed similar calcification of its wall, and at a point 1 cm. from its origin was a calcified plaque on which a considerable amount of adherent grayish-red, friable blood clot was seen.

Anatomical Diagnosis. Infarction of the heart with rupture through infarcted myocardium (posterior wall of the left ventricle). Hemopericardium. Coronary arteriosclerosis. Hypertrophy and dilatation of the heart.

Comment. Typical for this group.

Group IV. Coronary Sclerosis Only with Myocardial Fibrosis Only. CASE XVII.—M. M., a woman, aged seventy-six years, was brought by the police patrol to the Pennsylvania Hospital, April 23, 1914, with a clinical diagnosis of myocarditis. She had been sick for four days with epigastric and substernal pain, which at times had been severe. There was no history of dyspnea, edema, cyanosis or blood spitting. The heart sounds were weak and distant, but there were no murmurs. She arrived in "fair" condition, with some cough and pain in her left breast. An hour and a half later, before any further examination was made, she vomited slightly and suddenly stopped breathing.

Autopsy. (No. 1703, Dr. Bixby.) The pericardial cavity contained 500 cc. of fluid and clotted blood. On the anterior surface of the left ventricle, 1 cm. from the septum, and midway between the apex and base, was a linear opening, 15 mm. long, almost parallel to the septum, which communicated directly with the chamber of the left ventricle. On the external border were three irregular and quite superficial "cracks" in the pericardium. There was no sign of trauma. The heart weighed 270 gm., and had a moderate amount of superficial fat. The cavities were small. The muscle was very flabby and dark-red brown. "At the point of rupture the left ventricle measured only 1 cm." (presumably it measured considerably more at neighboring points). The internal opening was smaller than the external and partly covered by the papillary muscle. The right ventricle was also soft and flabby; the aortic valves slightly thickened. "The coronary vessels are somewhat harder than normal, and can be traced quite readily beneath the pericardium."

Anatomical Diagnosis. Hemopericardium. Rupture of left ventricle. Brown atrophy. Coronary and aortic sclerosis. Chronic passive congestion of lungs and spleen, fatty liver, chronic interstitial nephritis.

Histology. The pericardium contains much fat and a coronary vessel greatly thickened with connective tissue rich in cells. The muscle fibers are shrunken and wavy, but not fragmented or vacuolated. The cross striæ are not seen. The nuclei are large and well stained with considerable perinuclear pigment. The edge of the rupture is irregular with a thin layer of fibrin, and near the pericardium there is some infiltration with erythrocytes and leukocytes. There is considerable diffuse and focal infiltration of leukocytes, eosinophiles and lymphocytes. Some of the coronary arterioles are very thick walled, with almost obliterated lumen. Sections from the kidneys and liver showed several small collections of polymorphonuclears, and the spleen contained an unusual number of polymorphonuclears.

Histologic Diagnosis. Brown atrophy of the heart. Acute myocarditis. Splenitis, hepatitis and nephritis.

Comment. There is no evidence of coronary thrombosis or myocardial necrosis in this case, though the rupture seems to have been due to myocardial disease following coronary sclerosis. It is unfortunate that circumstances did not permit a more detailed study, so that the cause of the collections of polymorphonuclears and their relation, if any, to the rupture could be clarified. Their occurrence in organs other than the heart certainly suggests a pyemia which may have had an important connection with the rupture. The "cracks" in the pericardium are also of interest, even though their etiology and significance cannot be explained.

CASE XVIII.*—A woman, aged sixty-eight years, who had been in poor health for years, had a "fatty heart" for a year. The day of her death she felt much worse and vomited. Four hours later she felt so badly that she had to lie down; but in a few moments sat up, retched, threw herself back, and was dead.

Autopsy. The pericardial cavity contained 8 to 10 ounces of blood. On the anterior surface of the left ventricle, 2 inches from the apex and $\frac{1}{2}$ inch from the septum were two openings $\frac{1}{8}$ and $\frac{1}{4}$ inch long. On the internal surface one of these tears was hidden by a columna carnea. Grossly the heart did not seem fatty, but microscopically was said to be very fatty, the fibers breaking up longitudinally on slight violence. The aorta showed beginning sclerosis.

* This case was reported by Dr. W. W. Keen in the *Transactions of the Philadelphia Pathological Society*, 1874-1875, 5, 94, but is included here as opportunity has since offered to make a histological study.

Further dissection, fifty years later, shows that the left coronary is greatly narrowed by a calcified area, 2 cm. from the aorta, before the descending branch is given off. It is also noted that the apex suddenly decreases from 1 cm. to about 3 mm. in thickness and is very fibrotic.

Histology. In spite of the great age of the material it is still possible to make out many histological details. For instance, near the apex the replacement of large areas of muscle fibers by dense bands of fibrous tissue, and in other areas definite perivascular fibrosis are easily made out. As striations and nuclei are not visible, it is impossible now to tell whether or not any acute necrosis was present. From its present appearance there does not seem to have been much fatty degeneration.

Diagnosis. Hemopericardium. Multiple rupture of the left ventricle. Coronary sclerosis with apical scar of old infarct.

Comment. This is a very good example of the kind of case which earlier passed as rupture due to fatty degeneration; but which in the light of later knowledge is found to have occurred in a heart that is the seat of marked coronary sclerosis with resultant thinning of the apex and replacement with scar tissue. Clearly coronary disease was an important factor in its causation.

Group V. Coronaries not Mentioned. CASE XIX.—E. K., an Irish woman, aged seventy-four years, was admitted to the hospital, July 15, 1902, with a clinical diagnosis of myocarditis, complaining of joint pains for ten years. She had had the usual diseases of childhood. The short history described a fat, white woman, with a full slow pulse, muffled heart sounds, but no audible murmurs. On July 26 she died suddenly.

Autopsy. (P. G. H., 5855, Dr. Coca.) The autopsy showed 300 cc. of blood in the pericardial cavity. The heart which weighed 400 gm. was pale and friable and had considerable epicardial fat. At the auriculo-ventricular junction on the anterior surface of the left ventricle was a tear, the walls of which were infiltrated with blood so as to form a swelling, 2 cm. in width, extending along the auriculoventricular groove. The mitral valves were fatty and sclerotic. The aorta showed moderate sclerosis, but the coronaries were not mentioned. There was no histologic report.

Anatomical Diagnosis. Fatty degeneration and rupture of left ventricle.

Comment. The paucity of evidence in this case makes it impossible to tell if this was really fatty degeneration or an infarction following occlusion of the left coronary.

CASE XX.—E. F., a white woman, aged sixty-four years, was admitted to the neurological service of Dr. Potts, September 14, 1901, with a hemiplegia of two years' standing. She was also aphasic and incontinent both of urine and feces. She also had a large ulcerating carcinoma of the breast and axilla. The only mention of the heart was that the second aortic sound was rough. The urine was negative. She died, December 5, 1902.

Autopsy. (P. G. H., 5981, Dr. F. P. Gay.) Autopsy showed a large well-nourished woman with the aforesaid cancer. The pericardial cavity was found full of blood, and the surface of the heart covered with fibrin. The apex was firmly adherent to the parietal pericardium by fibrous adhesions. When the fibrin was removed two ragged openings were found on the anterior surface extending through the copious fat into the cavity of the left ventricle. The coronaries were not mentioned. Histologically, there was much fragmentation and segmentation and perinuclear pigmentation, more marked in the right auricle than in the left ventricle. The diagnosis was made of brown atrophy.

Comment. As the section taken was obviously not from the neighborhood of the rupture, it is not possible to say what the condition of the

myocardium was at this point. The apical adhesion suggests an organized infarct, which in turn suggests coronary disease. The occurrence of further coronary occlusion with rupture of the resulting anemic infarct is at least as probable as any other explanation.

CASE XXI.—A clubman, aged sixty years, and a moderate drinker, came to the office of Dr. B. F. Stahl one morning about 8 A.M., complaining of precordial pain. Very little was known about his general condition, except that he said that he was seldom sick. After a short examination which revealed nothing startling, he was sent home, where he died suddenly in about an hour. There was loss of sphincter control just before death.

Autopsy. The pericardial cavity contained much blood, which was found to have come from several small tears in the lower third of the left ventricle, some of which communicated with its cavity. No further details of the condition of the heart are available.

Comment. None.

CASE XXII.—A. U., an aged female, died at the hospital, October 29, 1868, after having been insane nineteen years. She was a very large, fat, flabby woman, with a weak heart, some cough and dyspnea, but no edema. The day of her death she complained of pain in her left side. That evening she suddenly fell over, and died in a few minutes.

Autopsy. (P. G. H., 72.) The pericardial cavity contained 12 ounces of dark blood and clot. The heart was not much enlarged, weighing $14\frac{1}{2}$ ounces, but was unusually flabby and covered with a fatty deposit. One inch from the apex of the anterior surface of the left ventricle, near the septum, was a tortuous irregular rent, $\frac{1}{3}$ inch long on the endocardial surface and partly filled with firmly adherent clot. Its edges were rough and jagged and the external fibers seemed more torn than the internal. The coronary arteries were not mentioned.

Histology. Marked fatty degeneration of the muscle fibers either with central loss of transverse striæ or complete loss of striation with granular degeneration. Only a few healthy fibers remained.

Comment. This seems more like rupture due to fatty degeneration than any case of the series, and yet in the absence of more detailed statements, especially about the coronaries, the question must be left undecided.

Clinical and Pathologic Data. The figures for the age, sex and site of rupture and, to a lesser extent, for survival after rupture are based on all of the 654 cases. The remaining items are based almost entirely on the cases abstracted by us. It is perhaps unnecessary to add that the items that we have attempted to investigate were completely reported by very few and in most cases only a small number were mentioned.

CLINICAL. *Sex.* Three hundred and four were males and 217 were females. This corresponds fairly well with the generally accepted view that males are slightly more prone to the accident, though Quain stated that in his series the two sexes were equal in this respect. He gave no actual figures. The predominance of the causes of arteriosclerosis in the male sex is doubtless responsible. In statistics of coronary sclerosis the preponderance of males is more marked,

TABLE I.—SEX DISTRIBUTION.

	Our analysis.	Quain.	Minet.	Robin.	Total.	Per cent.
Male . .	185	Considered	38	81	304	58.3
Female . .	112	Equal	37	68	217	41.7

Age. The average age at which rupture occurred was well in the sixties. The greatest number of cases occurred in this decade and the next greatest number in the seventies. When one considers how few persons relatively live to reach this age the results are truly astonishing. These figures confirm the opinion that spontaneous rupture of the heart is characteristically and strikingly a phenomenon of old age and suggest the fundamental importance of the condition of the coronaries. Particular interest attaches to the underlying cause of rupture in those patients who died young, and as one might expect, coronary disease no longer plays a predominant role. Of the 25 cases in our abstracted series under forty years there were 17 males to 8 females. Acute infection was a prominent factor in 9, lues in 5, trauma in 4, alcohol in 3, coronary disease in 2 and 3 doubtful. The auricles were more prominently involved; the left, 5 times; the right, 4; the right ventricle, 2; the left ventricle, 13; multiple tears, 2.

TABLE II.—AGE DISTRIBUTION.

Decennials.	Our analysis.	Quain.	Minet.	Robin.	Total.	Per cent.
Aged . . .	24	6	30	4.9
80+ . . .	12	6	13	21	52	8.6
70's . . .	63	24	22	58	167	27.7
60's . . .	99	33	19	37	188	31.3
50's . . .	47	13?	8	13	81	13.4
40's . . .	25	6?	4	8	43	7.1
30's . . .	12	3	2	6	23	3.9
20's . . .	4	2?	6	1.0
10's . . .	5	1?	2	..	8	1.4
1 to 10 . .	4	4	0.7
Total . .	295	88	70	149	602	

Habits, Occupations and Predisposing Causes. Pertinent statements about these items were obtained in less than one-quarter of the cases abstracted by us. All social classes were subject to attack. Forty-seven of them were insane, a remarkably high incidence that has been noted by others and for which we have no explanation other than the common factor of arteriosclerosis. Except for this and the frequency of intemperate habits (noted in 24 cases), it cannot be said that these items of our study contributed much of interest or value. Even the notation of intemperance is subject to two general fallacies underlying statistics, namely, that a comparison with intemperance in subjects whose hearts did not rupture is not feasible and that possibly the authors' attentions may have been unduly focused on this point. Syphilis was conspicuous by

its rarity, except in those dying under forty years. Twelve were noted as obese, though this number should undoubtedly be much higher.

Exciting Causes. These are manifold in the coronary cases and vary from severe to the slightest form of exertion: Eating, 14 cases; walking, 13; defecation, 10; while conversing, 5; getting out of bed, 6; emotional excitement, 5; at toilet, 5; trauma, 3; convulsions, 3; attack of angina, 3; violent exertion, 2; sitting up in bed, dressing and so forth, 9. Five were, as far as they knew, perfectly well until they suddenly fell over dead. Twenty-one died during sleep (including 1 of our own series), but according to recent work of MacWilliams, this is not a period as free from strain as one might suppose. Particularly during dreams or restless sleep he found marked changes both in the rhythm of the heart (heart block, etc.) and in the blood pressure (increase of 20 to 30 mm.), which might easily be sufficient to rupture a necrotic myocardium.

Premonitory Symptoms. Attacks of vertigo, cough, dyspnea, syncope and even hematemesis are said to be indicative of the prodromal stages of rupture. They were not at all conspicuous in the case reports we studied and certainly not more so than would be found in the equal number of several cardiac cases whose hearts did not rupture. Diarrhea and vomiting seemed to have somewhat more significance. Anginal pain, on the other hand, was obviously important, being noted 70 times (in 7 out of 9 of the Boston cases), but this should be interpreted rather as a sign of coronary disease than of impending rupture. We know of no way accurately to differentiate the two conditions from the point of view of this symptom. In fact it may be said that the early symptoms are chiefly those of coronary disease and that it is still impossible to predict which cases of coronary disease are to suffer rupture. In a fair number of cases no preliminary symptoms preceded the acute attack.

Terminal Symptoms. Death is usually so sudden that in many cases the person is seen merely to fall over dead or is found dead. This applies to the auricular as well as to the ventricular cases. In a single case, where the physician chanced to be at the patient's bedside when the rupture occurred, a peculiar rushing, roaring sound was heard through the stethoscope that had been immediately placed over the patient's precordium. If life lasts a few moments there are signs of acute collapse, with air hunger, pallor or deep cyanosis, with stertorous breathing, cold sweat, perhaps vomiting, convulsions or unconsciousness, and in the few cases in which the heart has been ausculted the sounds are faint but rhythmic, or absent and the radial pulse imperceptible. In the rarer type lasting a few hours or more the patient may have the usual signs of acute cardiac failure, cough, angina or increasing signs of chronic heart failure. The time that the patient survived after the rup-

ture had taken place is given in Table III, as well as it can be estimated. But the reader must realize that this table is no certain picture of the facts. In several cases where death was reported as occurring so many days to weeks, and even, in 1 case, to over a month after rupture, consideration of the history and actual course of symptoms reported lead us to the decision that the time given for the first occurrence of rupture really indicated a situation arising from sudden occlusion of a coronary, while the actual rupture probably took place at a much later date. In these cases we have taken the liberty of tabulating the period of survival according to our own interpretation of the symptoms, rather than after the original report. At the present time, after more careful study of the histologic sections taken from our own cases, we feel that we have perhaps erred in these later interpretations of symptoms, and that some of these cases may really have survived longer than we thought possible. The wide infiltration of blood and leukocytes, and in some cases even an apparent attempt at connective tissue formation, are conditions that take more than a few minutes to produce.

TABLE III.

Survival.	Our analysis.	Quain.	Minet.	Robin.	Total.	Per cent.
"Sudden"	178	71	31	8	288	72.0
Less than 10 min.	30	..	1	..	31	7.7
10 min. to 20 min.	7	..	1	..	8	2.0
20 min. to 1 hr.	3	3	0.8
1 hr. to 12 hrs. .	14	..	18	2	34	8.5
12 hrs. to 48 hrs. .	7	..	10	..	17	4.2
2 days to 8 days	3	..	10	..	13	3.3
8 days	6	..	6	1.5
	<hr/> 242	<hr/> 71	<hr/> 77	<hr/> 10	<hr/> 400	<hr/>

Mechanism of Death. This is still far from clear but probably varies with the size of the rupture and the consequent suddenness with which the pericardium is distended and the rest of the system deprived of its normal supply. For obvious reasons it is practically always impossible to make an accurate study in clinical cases. One might assume that cardiac arrest from the increasing pressure from the overdistended pericardium must play an important part, especially in the slow leaks that survive for some hours; but as Robin and Nicolle point out, some patients die with very little blood in the pericardium and cases of traumatic rupture are known to survive for a longer time than the spontaneous cases. On the other hand, Vance has recently shown in cases of traumatic rupture that if the escaped blood can drain into the pleural cavity death may be postponed for many hours. A second factor, especially in the sudden cases, is cerebral anemia, but to be so suddenly fatal the cerebrum must be deprived of more blood (perhaps by vasomotor action) than that lost into the pericardial cavity. The

terminal symptoms in some cases resemble those of fatal coronary thrombosis, where presumably cardiac arrest is primary; but others are more like those of cerebral syncope. Disturbance of cardiac mechanism, such as ventricular fibrillation, must also be taken into account.

PATHOLOGIC. Site. The site of the rupture was mentioned in almost every autopsy report. As will be seen in Table IV, the left ventricle greatly predominated and especially on its anterior surface. In Minet's and our series the anterior surface was involved 150 times as against 57 of the posterior, 38 of the apex and 5 of the external surface. Of 60 cases in which the location was further specified, the rupture was in the lower third in 35, in the middle third in 21 and the upper third in only 10. In traumatic cases, on the other hand, the left ventricle is less commonly involved than the right, on account of its less exposed position.

TABLE IV.—SITE OF RUPTURE.

	Our analysis.	Quain.	Minet.	Robin.	Total.	Per cent.
Right auricle	20	7	2	6	35	5.7
Left auricle	8	2	..	2	12	2.0
Right ventricle	32	13	5	13	63	10.2
Left ventricle	225	78	70	120	493	79.7
Miscellaneous	7	8	15	2.4
Totals	292	100	77	149	618	

The right ventricle is a poor second. Of the 32 cases of our series the anterior surface was involved 14 times (upper third, 1; middle third, 3; lower third, 6; not mentioned, 5); the lower third of the posterior surface, 2; the apex, 6; site unmentioned, 9.

The right auricle was ruptured 35 times (equally distributed over its various parts); the left only 12 times.

The 15 miscellaneous ruptures of the table were of the septum, apex (unqualified), or where the chamber was not designated. The reason for the predilection of the anterior surface of the left ventricle is chiefly that it is the descending branch of the left coronary that is most markedly atheromatous and most frequently thrombosed. The greater pressure in this chamber is undoubtedly an important contributing factor both to the rupture and to the greater amount of sclerosis. Discussion of the reason for the greater damage to the anterior coronary is hardly within the scope of this inquiry. As far as we know it has not been determined, but presumably the firmer support of the posterior surface by surrounding tissues would play a part.

It is noteworthy that the average age of those dying from rupture of an auricle was much less than that of the ventricular cases. In our series only 6 out of 25 cases of auricular rupture were over sixty years, with an average age of forty-three years, and in Robin and Nicolle's, 4 out of 10 with an average age of forty-seven years.

The non-coronary origin of the early deaths has already been discussed and of course the same factors apply here as well.

Character of Tear. In 223 cases in which the size of the rupture was given 60 (27 per cent) were less than 1 cm. in length, 5 of these were just large enough to admit a probe and 20 were less than 5 mm. in length. Sixty-four (28.7 per cent) were between 1 and 2 cm. in length; 43 (19.3 per cent), between 2 and 3 cm.; 24 (10.8 per cent), between 3 and 4 cm.; 17 (7.6 per cent), between 4 and 6 cm.; 15 (6.6 per cent), between 6 and 8 cm. The width (mentioned in 10 cases) varied from 2 to 25 mm., with an average of 8 mm. In 25 out of 36 cases the internal opening was given as smaller than the external; in 9 it was larger and in 2 equal.

The nature of the tear was mentioned in 166 cases and varied considerably. The edges were irregular or jagged in 72, clean cut in 20 and infiltrated with blood in 24. Linear tears were frequent, and described as oblique in 22, longitudinal in 18, transverse in 2, tortuous in 9, curved in 4, angular in 3, oval in 5, triradiate in 4, valvular in 1 and in 1 the apex had been pathologically amputated and lay free in the pericardial cavity.

The great majority (269) of cases were complete ruptures of a wall of the heart, producing large hemopericardia. In 8 of these, however, there was no mention of fluid blood or clot in the pericardial cavity. In 1 this was due to the rupture extending through an adherent diaphragm to the abdominal cavity. Presumably most of the others were the omissions of an incomplete report. Reports of partial ruptures were for the most part discarded. However, to get some idea of their usual position and cause, the first 16 cases met with were preserved. Of these, 4 were ruptured septa and 6 were papillary muscles. Of the other 6, 1 was a ruptured parasitic cyst (without blood in the pericardium); 1 showed separation of the auricular fibres without actual rupture (small amount of blood in pericardium); 1 ruptured into a coronary vein; 3 of varying depths from the pericardial surface did not reach the heart chamber (all showing blood in the pericardium).

Underlying Cause. The investigation of the cause underlying the rupture was considered by us to be one of the most important topics of the inquiry; but the incompleteness of many of the pathological reports has made it one of the least satisfactory. Thus, early impressed with the importance of the condition of the coronaries in this respect, we examined each report carefully for a statement about them, and yet in 156 out of 307 cases they are not mentioned—a fault by no means confined to the earlier observers. In fact even in the 22 cases now reported by us for the first time, in 4 it was impossible to get a statement about the coronaries. In Table V is given the results as best they can be tabulated, in the face of such difficulties. The largest group—fatty degeneration—is recruited chiefly from the older cases and undoubtedly contains

many—perhaps even a large majority—that today would be given different and more accurate designations.

TABLE V.—APPARENT EXCITING CAUSES.

	Our analysis.	Quain.	Minet.	Robin.	Total.	Per cent.
CONDITION OF CORONARIES GIVEN.						
Coronary thrombosis	74	6	51	24	145	23.8
Marked coronary disease with various myocardial lesions	68	1	..	44	113	18.5
Cause not determinable, coronaries approximately normal	9	2	11	1.8
CORONARIES NOT MENTIONED.						
Cause not determined	41	..	10	17	68	11.1
Heart apparently normal	4	1	5	0.8
Fatty degeneration and infiltration	59	77	15	35	186	30.4
Softening*	18	24	42	6.8
Thinned walls (aneurysm and fibrosis)	28	4	32	5.2
Syphilis	3	..	1	1	5	0.8
Tuberculosis	1	1	0.2
Parasitic cyst	1	1	2	0.4
Tumor (melanotic sarcoma)	1	1	0.2
					611	

Of the 151 cases of ruptured heart in which the condition of the coronaries is mentioned, they are said to be more or less diseased in all but 9. This would perhaps be expected where the average age is so high, but assumes a different and important aspect when coupled with the fact that in 74 cases actual thrombosis of the coronary had occurred and that in 32 more the coronary disease was sufficiently severe to cause either marked thinning of the ventricular wall (with or without aneurysmal dilatation, 20 cases) or acute or chronic myomalacia (organized infarct, 8 cases). Of the remaining 29 cases, coronary disease was associated with fatty degeneration in 12; sclerosis, brown atrophy and so forth, in 8; no other condition mentioned in 9.

In 157 cases the condition of the coronary arteries was not mentioned. In these cases also it was, of course, more difficult to appreciate the exact condition of the myocardium, on account of differences in terminology and conception of disease a generation ago. Thus "fatty degeneration" was a very popular term, which, based on gross inspection only, was probably frequently used incorrectly to describe acute infarction as well. In this group, for instance, it occurred 59 out of 157 times (37 per cent), while in the first group only 19 out of 151 times (12.6 per cent), 7 times associated with coronary thrombosis and 12 times with other forms of coronary disease. Continuing with the second

* This group includes indefinite descriptions such as apoplexy, red softening, ulceration, gelatinous, degeneration, etc. Doubtless many were really infarcts, others merely flabby or fatty and a few true abscesses.

group, "ulceration" was the assigned cause in 8 cases, and we suspect that this included some cases of infarct; infarct, as such, was given only 7 times. In 23 cases the ventricular wall was described as locally thinned to such a degree that it was obvious that the condition at least approximated cardiac aneurysm following coronary disease. Among the other assignable causes were fatty infiltration, 6 cases; fibrosis, 5 cases; syphilis, 3 cases; abscess, 3 cases; brown atrophy, 2 cases; parasitic cyst, tuberculosis, melanotic sarcoma, each 1 case. In 41 cases no cause was assignable, and in 4 the heart musculature was said to be normal. Without adequate histologic examination, however, this statement is of little value, and spontaneous rupture of a normal heart wall is properly questioned.

What a different picture these figures give from the usual textbook description of the underlying pathologic lesions of ruptured heart! Consideration of the two groups permits the conclusion that spontaneous rupture of the heart wall is due in the great majority of cases to antecedent coronary disease often with actual thrombosis, causing either an acute infarct (acute myomalacia) or organized infarct or such a poor state of nutrition that the muscle fibers degenerate and the thinned wall stretches to form a cardiac aneurysm. In the latter case rupture seems to occur either with or without a terminal necrosis of the muscle fibers. The small remaining minority is to be accounted for chiefly by acute and chronic infectious processes.

General Condition of the Heart. Apart from the condition of the myocardium at the site of the rupture, the most striking feature was the excessive amount of subpericardial fat, which was especially noted in 58 cases and was a prominent feature in most of the cases personally observed by us. It is noteworthy that the myocardial fibers were usually better preserved just beneath the pericardium than they were at other levels. So-called fatty degeneration was noted 34 times and the heart called pale and flabby (and often greasy), 25 times. Brown atrophy was noted 7 times; myocardial degeneration, 6; myocarditis, 4; fibrosis, 4. The heart was usually said to be enlarged. In 34 cases in which we have noted the weight, it averaged 433 gms. (270 to 870 gms. as extremes).

Discussion. It seems, then, that a person dies from a broken heart, not in young adult life from a great grief or emotion, but usually in old age, on account of diseased coronaries and from such immediate prosaic causes as walking, eating, defecation, slight exertion, or even during sleep. The condition was first described, as far as we can learn, by William Harvey, who also observed precordial pain in his patient and at autopsy found "An impediment to the passage of the blood from the left ventricle into the arteries." Morgagni (who himself died from it) described it in an old woman, aged seventy-five years, who had the traditional fatty heart.

Among its distinguished victims were George II (during defecation, Elleaume), Morgagni, the Scotch Dr. Abercrombie, Admiral Villeneuve, who after his defeat by the English was said to have committed suicide by lacerating the right auricle with a needle introduced between the ribs.

The underlying causative agents are reasonably well known, though it is far from clear why following coronary thrombosis, for instance, some infarcts should rupture and others go on to organization. The exciting causes also show a dissatisfying diversity that can only be partly accounted for by our inability to say exactly when the rupture occurred. One would naturally think that the accident would be especially associated with conditions causing increased intracardiac pressure; yet granted that this may occur at such unlikely times as during sleep, as has been previously suggested, still many other cases occurred after quite trivial movements or during absolute rest. Presumably the progress of the necrosis plays a more important part (compare our second case with liquefaction necrosis). Though apparently in some cases the functional weakness may be operative before the usual microscopic signs of necrosis are visible (Case X).

The actual method of production of the rupture is still open to discussion. Apparently some ruptures progress from the inside out and more *vice versa*, depending on which zone or layer the most necrotic and weakest focus happens to be in. From the post-mortem appearances most are produced suddenly with rapid out-pourings of blood (is this begun in systole or diastole?); but some, with sinuous, thrombin-covered walls, undoubtedly have progressed much more slowly.

The symptomatology is not characteristic and difficult to separate from that of coronary thrombosis, and the time available for study is usually very short. The diagnosis is therefore seldom made antemortem, and doubtless many cases of sudden death in the aged have had unsuspected ruptures. Terminal progressive increase of precordial dulness might in rare cases permit a correct diagnosis. In a few cases it has been made before autopsy, if not before death.

This is of no great matter, however, as the prognosis of a complete rupture is, as far as we know, invariably bad, and no method of treatment has been found to be of any use. It is, of course, possible that very tortuous minute passages might be blocked spontaneously by a clot long enough to permit organization or adhesion to the parietal pericardium to take place, and this possibility becomes more probable in the partial tears. As regards surgical intervention, in view of the diseased state of the myocardium, it is hardly conceivable that suture would be of any use, even if the correct diagnosis were made in sufficient time.

Study of the morbid anatomy brings out several interesting

moot points. The postthrombotic infarct, the organized thrombus, septic foci and so forth need not be further discussed here. The frequent concurrence of marked fatty deposit in the pericardium is curious, but its relation to the rupture obscure. The great diversity in the character of the tear and the variable relative size of the internal and external openings are indications that the mechanism of rupture differs in different cases, but offer no clue to solve this question. Another curious observation is that the internal opening has not infrequently been found partly hidden behind a papillary muscle, where it would seem to be relatively well protected. The case in which rupture occurred in an area supplied by a recently thrombosed artery, but not showing visible signs of necrosis (our Case X) indicates that functional weakness can be manifest before signs of structural change. It must be recognized also that coronary thrombosis may occur without signs or symptoms, that considerable myocardial necrosis may occur without coronary thrombosis (Cases XII–XVI) and that following coronary thrombosis the myocardium may at autopsy appear normal, even to the trained pathologist, and yet histologically show considerable necrotic and infiltrative changes (Case I).

Some of these question will undoubtedly be solved by future clinicopathologic observations; others can perhaps be better attacked by carefully planned animal experimentation.

Summary. From analysis of 22 cases hitherto unpublished, and 278 cases reported by others, and from a survey of 354 further cases from the literature (totaling 654), the following conclusions may be drawn:

Spontaneous rupture of the heart is chiefly an accident to the left ventricle of the aged; in the aged it is practically always due to coronary disease. It most frequently occurs in an acute infarct of the anterior surface of the left ventricle following sudden thrombosis of an artery or one of its branches; or less frequently the infarct may follow gradual fibrotic occlusion of the lumen.

With severe coronary sclerosis and consequent myocardial degeneration (usually with more or less cardiac aneurysm), rupture may occur in an area not obviously necrotic and supplied by a patent artery. The bursting of a cardiac aneurysm has been observed, but is rare. Evidence is presented to show that the formerly popular diagnosis of fatty degeneration is usually incorrect or open to serious question.

Other rarer causes of spontaneous rupture considered in this analysis are "ulceration," fatty infiltration, fibrosis, syphilis, abscess, brown atrophy, parasitic cyst, tuberculosis, melanotic sarcoma. Most of these are based on reports of little value on account of the antiquity or incompleteness of the data.

Evidence about the site and character of the tear is considerable and accurate, but the actual mechanism which produces rupture and the actual cause of death are not clearly understood.

All classes and occupations are liable and the exciting causes are most diverse. Premonitory symptoms are frequent but not characteristic. Terminal symptoms are usually so abrupt that little treatment can be even attempted and the antemortem diagnosis is seldom made.

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RELATION OF MORPHOLOGY TO THE PROGNOSIS OF AORTIC SYPHILIS.*

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LAST year Scott reported a series of 25 cases of syphilitic disease of the aorta and of the aortic valves. The clinical picture was one of aortitis and aortic regurgitation, and the study was enhanced by the fact that autopsies were held on all of the cases, confirming the clinical findings. Several of the observations made by Scott are worthy of repetition. The cases presented the picture of aortic regurgitation with cardiac failure; the symptoms were not those usually associated with aortitis, such as substernal pain and nocturnal paroxysmal dyspnea; they lived for only a period of months after the onset of symptoms of cardiac failure, and the treatment seemed to be of little value. At autopsy it was noted that the aortitis merged into thickened, fibrosed, distorted aortic leaflets which produced an incompetent orifice and at times demonstrable narrowing or occlusion of the coronary openings was observed. These morphologic findings readily explain the serious prognosis in this group.

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We agree with Scott that the cases he has described represent a form of syphilis of the aorta and aortic valve commonly seen in hospital practice; moreover, it has been our experience, also, to see a rapid downward course in the majority of this type, although a few live from one to two years. We have never been impressed by the response they made to antisypilitic treatment, although temporary relief of symptoms has followed the use of therapeutic measures, as Longcope noted some years ago. As this group represents a highly fatal form of aortic syphilis in a relatively short period of time, and as there appears to be among clinicians a growing tendency to regard this form as the only picture of the disease, we consider that some attention should be directed to other phases of the process in this location. There is another class of aortic syphilis which differs from that just mentioned, and which forms, in a way, a group showing some variations in its morphology, clinical features and in the response to treatment. The point of differentiation depends upon the fact that in more than half of the cases of aortitis observed at autopsy the aortic cusps are normal and the aortic orifice is intact. The development of a regurgitation may indicate a dilatation of the ring and not necessarily any valvular involvement. This holds true even when the aortitis has reached the stage of aneurysm development. Longcope has spoken of this in his excellent article on aortitis. The signs and symptoms are usually those of aortitis and not of cardiac failure. The duration of life is longer and it is our belief that antisypilitic treatment is in some cases at least very effective in prolonging life. We wish to make a few remarks about this group, particularly with reference to one of the terminal manifestations of aortitis, namely, aneurysm. What pertains in-general to the last stages of the process in the aortic wall in regard to prognosis would hold true for the earlier periods of the disease, but to a greater extent.

The morphologic pathology of the aorta is well known, particularly those changes which we believe to be due to syphilis, so it is not necessary to refer to it in any detail. One or two points, however, we desire to mention. The granulomatous process commences, as a rule, about $1\frac{1}{2}$ inches above the aortic orifice and extends along the aortic wall to near the diaphragmatic opening. It may, but does not usually, go beyond. The lesion is frequently localized by almost abrupt lines at its beginning and end in the thoracic aorta. It is obvious that certain variations occur within these limits. It would seem that the ascending aorta is the most frequent and earliest part involved, and one would imagine that there should be a reason why the process does not spread down to the aortic valve, a distance of 1 to 2 inches, as readily as it reaches the more distant arch and descending thoracic portions. To be sure, the aortic valves are involved in a certain percentage. We believe it to be less than half. McCrae and Longcope have referred

to the dilatation of the aortic orifice, a condition which we regard as being more frequent than is generally considered. Klotz has suggested this peculiar distribution to be due to the fact that the spirochetæ reach the wall of the aorta by way of the lymphatics, and the first 1 to 2 inches of the aorta is not supplied by numerous lymphatics, as are the other portions where there is such abundant lymphoid tissue adjacent.

Microscopically in the wall of the aorta in aortitis or in aneurysm one sees varying stages of the granulomatous process as gummy necrosis on one hand and healed fibrosed lesions on the other. We would emphasize this latter point, namely, signs of spontaneous healing are evident. This process, moreover, may be so well developed as to very occasionally lead to a completely healed or latent aneurysm. True it is that such an end result is rare; but it is nevertheless an autopsy finding. Many museums have such specimens. Osler has spoken of the healing of some saccular aneurysms. Fibrous tissue is the principal element in this healing process. It is interesting in this connection to refer to what one might well term experimental aneurysm production from the work of C. C. Guthrie on the transplantation of segments of the wall of the inferior vena cava to the carotid artery in dogs, done a number of years ago. In one of these dogs he noticed that about a month after transplanting the piece of the wall of the inferior vena cava into the common carotid, an aneurysmal dilatation about the size and shape of an English walnut appeared and remained as such for the rest of the dog's life, which was eleven years. The animal during this time had two litters of pups, and was in several laboratory disturbances, so that one could freely say that the dog lived a normal life. Death was due to a hypernephroma with general metastases. Guthrie, Klotz and Permar reported the aneurysmal condition of the carotid, the wall of which was composed of fibrous tissue. Although the conditions here are not exactly the same as in the human aneurysm of syphilitic origin, in that inflammation is absent, yet the experiment does suggest that fibrous tissue is able to transplant the muscular wall of a large vessel and to assume its function quite readily. The same factor must be present in those cases of spontaneously healed or latent aneurysms of the aorta in the human, where it is very probable that the walls of the aorta are little more than fibrous tissue and that there is no active or progressive inflammatory reaction present. We are referring to this type of aneurysm not as an entity in the problem of prognosis on account of its rarity, but merely to indicate that fibrous tissue is capable of replacing the musculo-elastic wall of the aorta in a condition which has once been the site of an active inflammatory change. The development of a good fibrosis in the wall is the chief hope of prolonging life in aortitis with aneurysm.

An attempt to transfer this idea of healing by fibrosis with good

functional results to the clinical study of aneurysm of the aorta is another matter. Past experience would seem to point directly to failure, although prolongation of life is at times attained. In this connection the statistics of Boyd are of some interest in that the length of life of patients with aneurysm may extend over a considerable number of years. In 830 cases 20 per cent lived more than two years; 10 per cent over four years; 5 per cent over six years; 3 per cent over eight years and 2 per cent over ten years. It would appear that a regurgitant lesion at the aortic area, especially if due to involvement of the valves, tends toward a much shorter duration of life. In Scott's group it was nine months; but as this represents the average, there were undoubtedly some that lived considerably longer than this figure would indicate. Willius, in 167 cases of aortic regurgitation due to syphilis, found the duration of life to be fifteen months after their initial examination at the clinic. As the onset of symptoms in this type of aortic syphilis, as Scott has shown, is often very abrupt, these figures also fairly closely represent the duration after the appearance of the first clinical manifestations.

Several problems arise and some of them can only be solved by a large series of cases over a long period of time. The important and obvious point to be decided is the problem of dealing with the spirochetæ in the aortic wall. Can the organism be killed *in situ*? If this is possible the granulomatous inflammatory reaction will be replaced by fibrous tissue, or, in other words, healing will occur. It may be safer to assume that all we can hope to do would be to put the spirocheta into a latent state so that the inflammatory process does not progress. Under these conditions fibrosis might also develop, which would further protect the wall of the aorta. It is, moreover, likely that the older and more widely distributed lesion would offer much less change of a favorable response than the earlier or smaller process. Further, if the inflammatory process in the aorta is of the type which does not involve the aortic cusps, or has as yet produced no evidence of dilatation of the aortic orifice, the factor of regurgitation is not added and the possibility of a prolongation of life made much greater. The treatment employed must include the usual antisypilitic measures and a prolonged rest. We have seen no ill effect from the careful use of arsphenamin or neoarsphenamin, but they are of much less value and may be even dangerous in those aneurysms having an aortic regurgitation. Certain aneurysms are, therefore, ruled out as not being suitable, because these cases are virtually the same as the group described by Scott; not a great deal can be done for them, although symptomatically improvement at times follows treatment.

We have had some experience with the medical treatment of aortic aneurysm and reported our findings in 3 cases five years ago chiefly because of the clinical improvement noticed. As 2 of these

cases are still living and in apparent good health it has seemed worth while to review some of the important points in their histories. One of the cases has been under our observation for almost nine years (eight years, ten months), the other about seven years (six years, ten months). The third case died about two and a half years after we first saw him, and it may be worth emphasizing that in his case a well-recognized aortic regurgitation with cardiac symptoms was associated with the aneurysm.

Case Reports. CASE I.—A man, aged thirty-six years, a molder, entered the Mercy Hospital in August, 1916, suffering from very severe choking attacks which occurred at night and were associated with considerable substernal pain. These symptoms had been present since June, 1916, or six weeks prior to his admission. He was perfectly well before that time. The attacks had become more frequent and the pain was more severe. Before his admission to the hospital they were occurring on three or four nights during the week. He had two attacks during the first week in the hospital, but these were the last. He had been working steadily at his trade, which was a fairly severe physical test, without any evidence of shortness of breath other than the attacks just described. In his past history there was very clear evidence of a primary sore fifteen years before the onset of the present symptoms.

The physical examination showed a very apparent pulsation in the first and second interspaces on the right and in the episternal notch, with a distinct lifting of the sternal end of the right clavicle with each pulsation. An expansile character was noted by palpation at this area. There was increased dullness to the right of the sternum above the level of the upper border of the third rib. On auscultation the heart sounds were regular, the aortic second was tympanitic and over the aortic area transmitted to the clavicle a systolic murmur was heard. There was no evidence of aortic regurgitation. By fluoroscopic examination an expansile pulsation in the aortic bulging was clearly seen. The plate showed an enlargement of the ascending aorta with a saccular-like bulging where it curved into the arch. The rest of the physical examination showed nothing of note. The Wassermann reaction was positive.

The following treatment was carried out: The patient was kept in bed for six weeks. During this time he was given daily inunctions of mercury (1 dram a day) and moderate-sized doses of potassium iodid (gr. 15, three times a day). After one week he was given six injections of arsphenamin in dosage of 0.2 gm. It was diluted to at least 100 cc. Following his discharge from the hospital he took one month of almost complete rest at home, and during the following month he had four injections of arsphenamin of the same amount, and this was the final number. He took mercury steadily for three years by the inunction method, resting two weeks in every two months. During the fourth and fifth year he was given mercury over a period of one month in every three. We have every reason to believe that he carried this out faithfully. At the end of three years his Wassermann was negative, and it was the same on the following year. During the winter of 1917 and the greater part of 1918 he was making 130 pound shells, and in the course of his work had to lift this weight from one hundred to one hundred and twenty times a day. The reason for this foolhardy procedure, because we had warned him against hard physical labor, was an economic one. Shellmaking was very remunerative work, particularly for a skilled workman. He, however, appeared to be none the worse for this test, but since then has done much lighter work. In 1919 he fell off

a ladder and broke one of his ribs, but he noticed no discomfort referable to the substernal area. The physical signs almost five years after showed the widening of the aorta, the systolic murmur and the tympanitic aortic second sound. The pulsations, however, were not visible on inspection. At this time, which was our last examination, he admitted that he felt as well as he had ever been, and he looked the part. For the past four years he has been living in California, but he has reported regularly every year by letter. He manages a garage, and according to his own recent statement he feels perfectly well and works every day. We have, therefore, not had the opportunity of examining him during this period.

CASE II.—A man, aged thirty-five years, laborer, entered the Mercy Hospital in July, 1918, suffering from intense substernal pain which forced him to sit up in bed or in a chair most of the night for several months. His symptoms dated back for a period well over a year. He complained also of some coughing, but the pain was the chief symptom. On physical examination the diagnosis was at once evident by inspection of the chest. There was a round swelling in the second right interspace just beyond the sternal border 4 cm. in diameter and protruding 2 cm. above the chest wall. This mass could be seen to pulsate and on palpation the expansile character was evident. There was a broad area of dulness on percussion and a systolic murmur was heard over this area. There was some question as to whether a diastolic murmur was evident at the aortic orifice. Our notes indicate "slight regurgitant aortic lesion," but the second sound is described as being ringing. McCrae has called attention to this in conditions of dilatation of the aorta and aortic ring. Later observations indicated no diastolic murmur. The Roentgen ray showed a very large aneurysm involving apparently most of the thoracic aorta. Under the fluoroscope it was expansile. The heart was not enlarged and its rhythm was regular and of good quality. The Wassermann was positive.

It appeared to us at first that treatment in this case could only be futile; but after two weeks in bed, under the usual iodid and daily mercury inunction, symptoms were considerably relieved and we decided to proceed with the other antisyphilitic therapy, arsphenamin. He remained in bed for the greater part of sixteen weeks, and during this time was given daily inunctions of mercury and ten intravenous injections of arsphenamin of 0.2 gm. and four of 0.3 gm. At the end of this time he left the hospital with instructions to take mercury by mouth and potassium iodid. We knew he would not carry out the inunctions at home. On leaving the hospital his symptoms had disappeared and the mass which had protruded from the chest was also gone, but one could still feel in the second right space the expansile pulsation.

This patient was very difficult to manage and extremely difficult to follow after he went home. He returned for examination in about fifteen months. He was feeling very well and was working. There was no indication of recurrence of the protrusion of the aneurysm. He had had no pain. Otherwise the signs were about the same. There was no aortic regurgitation. He had taken no further treatment after leaving the hospital.

We have seen him on two occasions since that time. In 1922, on examination, we found the physical signs to be about the same as when he was discharged. There was no regurgitation and the aneurysmal sac appeared to be about the same size. It was not evident on the surface at the side of the sternum. His Wassermann reaction was strongly positive. He told us that he was free from symptoms except for an occasional cough. Our last examination, a few weeks ago (1925), showed a very different picture. The sac of the aneurysm was again visible at the side of the

sternum, appearing as it was when he was first admitted to the hospital in 1918. Further, a very evident aortic regurgitation was noted and the heart was considerably enlarged. Coughing was the only symptom he complained of, although he apparently suffered at times from substernal discomfort. He had, however, been working steadily at a light occupation. With the exception of the treatment which he had while in the hospital, in 1918, it is probable that he had not taken mercury for more than two of three months during these years. We could not get him to coöperate.

CASE III.—A man, aged forty-two years, was admitted to the Mercy Hospital in August, 1918, suffering from nocturnal dyspnea and severe, almost constant, deep thoracic pain. In addition to this, on the slightest exertion he became very dyspneic. These symptoms had been present in some degree for a year and a half prior to his admission. There was no edema of the extremities, the liver was not palpable and the lungs were clear. Compensation appeared to be good. A diffuse throbbing pulsation over the whole upper chest and in the vessels of the neck was evident. Dulness was increased on both sides of the sternum above the cardiac area, particularly on the left side. A tracheal tug was present. There was a double murmur at the aortic area and some enlargement of the heart to the left. By Roentgen ray a large aneurysm involving the thoracic aorta was evident. The Wassermann reaction was positive. There was a history of a primary lesion twenty years previous to admission.

The patient rested in bed for a month, as he was unable on account of business responsibilities to take a longer rest. He was given potassium iodid and mercury in the usual manner, and he continued to take these drugs for about two and a half years. One month after beginning the inunctions he was given at weekly intervals six injections of arsphenamin, 0.2 gm., and after a period of one month three injections of 0.3 gm. at weekly intervals. This amount was repeated on the following month, so that in all he had twelve intravenous injections. He showed very marked improvement in that his symptoms were almost completely relieved, and during the first year and a half he put on 20 pounds in weight.

He worked steadily, managing his own hardware store, and reported on several occasions that he was feeling quite well. While waiting on a customer he fell over dead, which was about two and a half years after admission to the hospital. The suddenness of his death, in view of the coronary involvement that Scott has shown in his cases, would suggest that this was a possible explanation, although the sudden deaths due to myocardial changes described by Warthin must be remembered.

Discussion. There are certain points which these cases bring out, and they may, therefore, be briefly repeated: In the first the condition was recognized and treated very shortly after the onset of symptoms. The lesion was of the saccular type and had not developed to a large size. There was no clinical evidence that the process in the aorta had extended to the aortic orifice or to the valves, producing a regurgitation, and, therefore, the picture was never one of cardiac failure but of aortitis and aneurysm. If the antiluetic treatment in this patient has had any influence on the subsequent course of his disease, we believe the intensive and long use of mercury has been the most essential factor. He followed this faithfully for five years.

The second case illustrates a large aneurysm which, according to very definite symptoms, had existed for at least a year and a half prior to his appearance at the hospital. This aneurysm, therefore, has been present well over eight years. We are inclined to feel that the regurgitation at the aortic orifice in this instance is due to a dilatation of the ring. If we have accomplished anything in treatment it was done during the sixteen weeks he was in the hospital, for he has taken little or no treatment since that time. We would emphasize, also, the value of rest in bed. To prolong life over a few years in an aneurysm of this size should give some reason for hoping to do more for those seen earlier in their development. However, there are factors to be considered other than the actual size of the aneurysm, as the condition of the cardiac leaflets, coronary orifices and heart muscle, and its situation in the chest with reference to pressure on certain vital structures.

Our last case illustrates the type associated with aortic regurgitation, having clinical signs of cardiac failure and also of aortitis. This patient indicated the symptomatic relief which sometimes follows treatment even in advanced disease.

The prognosis in aortic syphilis has, therefore, some relation to the response to treatment, and the earlier the lesion is treated the better the result should be, although we frankly admit that it is a very difficult matter to be at all certain as to how much we have actually done by our therapy in the cases stated. Unfortunately, however, aortitis may, and probably does in the majority of cases, exist for a long period of time without producing any symptom which would lead the patient to his physician. Consequently an almost end result is presented even when the symptoms have been of short duration. This is true of the cardiac type that Scott describes and also of those forms which eventually develop aneurysm. Our first case illustrated this point very well, as his symptoms were present for only six weeks, although the process had undoubtedly been developing since his primary lesion fifteen years prior to that time. If this condition of aortitis is to be treated early its recognition by physical examination, serology and Roentgen ray must be far in advance of the onset of symptoms. More attention to the routine examination, especially of the aortic area, and routine serology are probably our best methods of approaching this problem of early diagnosis. Aortitis can be recognized by physical signs before any symptoms occur. These are well known, having been described in detail by McCrae.

Summary. 1. Syphilitic aortitis is most commonly localized in the thoracic portion of the aorta.

2. At times syphilitic aortitis is associated with aortic regurgitation, due to the process spreading from the aorta to the aortic ring or the aortic valves.

3. Syphilitic aortitis may be complicated by aneurysm formation. Some aneurysm cases are associated with an aortic regurgitation.

4. The occurrence of aortic regurgitation adds a grave factor to the prognosis of syphilitic aortitis.

5. Syphilitic aortitis, even to the stage of aneurysms, should be given specific treatment. Symptomatic relief nearly always follows, and it is possible that occasionally life may be prolonged for a considerable number of years in those cases where the process follows the usual morphologic distribution in the aorta, namely, noninvolvement of the valves, orifice or the first $1\frac{1}{2}$ inch of the aorta.

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THE NEUROLOGICAL MECHANISM OF ANGINA PECTORIS AND ITS RELATION TO SURGICAL THERAPY.*

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IN the surgical treatment of angina pectoris there has been surprising vagueness as to rational indications for the various operations employed. Ablations of different nerves and ganglia of the autonomic nervous system have been carried out, in some cases, with no apparent working hypothesis as to the relation of those nerves to the heart. The two cases reported below throw new light on this relation and make possible what would seem a more satisfactory explanation of the nervous mechanisms involved in angina pectoris.

The sympathetic nervous system has usually three direct connections with the cardiac plexus, the superior, middle and inferior cardiac nerves. All carry motor impulses to this plexus (Fig. 1). The superior cardiac nerve probably carries most or all of the constrictor fibers to the coronary vessels and aorta, as maintained by Ransom.⁷ The middle and inferior cardiac nerves are called by Langley⁹ the minor and major accelerators of the heart. Although

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all three nerves carry motor fibers, only the lower two contain sensory fibers from cardiac plexus to sympathetic ganglia (Fig. 2). These afferent impulses reach the central nervous system through

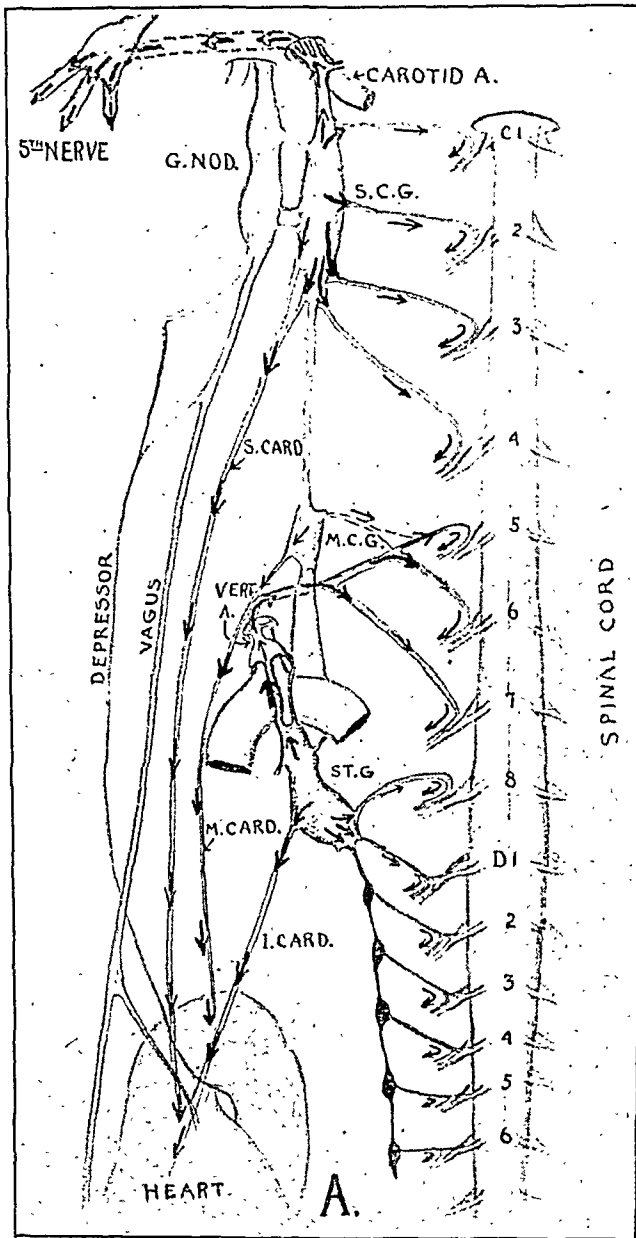


FIG. 1.—S. C. G., superior cervical ganglion of the sympathetic; M. C. G., middle cervical ganglion; St. G., stellate (inferior cervical and upper thoracic) ganglia; S. Card., M. Card., I. Card., superior, middle and inferior cardiac nerves; G. Nod., ganglion nodosum. Directions of motor discharges from sympathetic ganglia indicated by arrows. Gray rami accompany the spinal and trigeminal nerves without entering the central nervous system. An intermediate ganglion which is usually present is seen on the vertebral artery.

the rami communicantes to the upper six thoracic spinal segments (Fig. 2). It was shown by Langley⁹ that stimulation of the superior cardiac or the cervical sympathetic trunk produced no reflexes in

animals when the connection between vagus and superior sympathetic ganglion was cut, whereas stimulation of the two lower cardiac nerves produced reflex response as long as there remained a pathway to the central nervous system along one of the six upper thoracic rami communicantes. Dogiel showed there were sensory

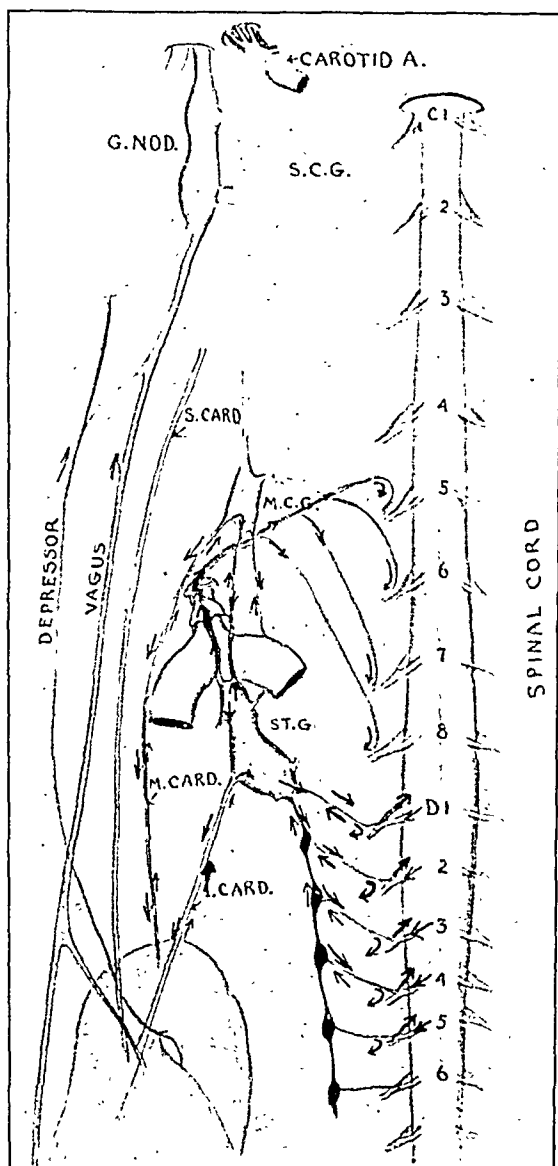


FIG. 2.—Arrows indicate direction of afferent impulses from cardiac plexus to central nervous system.

as well as motor endings in bloodvessels, although that does not mean that these fibers are true pain conductors. He pointed out that these sensory fibers³ were provided with thin myelinated sheaths and Edgeworth⁷ found that histologically fibers of this type all pass up into the central nervous system by way of the rami com-

municantes of the upper thoracic segments and by the vagus, an observation verified by Ransom. Thus there is good physiological and histological evidence to show that the afferent paths from heart to central nervous system pass by way of the middle and inferior cardiac nerves and the vagus; also, that the superior sympathetic ganglion is not a station in this path.

In the light of these anatomical findings, the rationale (or lack of it) for the various operations performed appears evident. Jonnesco⁸ removed the lower part or all of the chain in order to eliminate all afferent paths through the sympathetic. Hoffer⁶ cut a branch of the vagus which he believed to be the depressor, to eliminate vagus afferents, and Coffey and Brown¹ removed the superior sympathetic ganglion because it was easily accessible. Ransom has suggested that this last operation may prevent reflex spasm in the coronaries and aorta.

As I shall take up the following cases only from a neurological point of view, it is sufficient to say that the first patient, G. C., had a syphilitic aortitis with aortic insufficiency. The angina pectoris was severe and completely incapacitating. It began in the manubrium and spread to the inner aspect of the left arm. If not checked by nitroglycerin, it then spread to the inner aspect of the right arm.

According to the theory of referred pain, as first suggested by Head⁵ and Mackenzie,¹¹ a stimulus passes from the heart via the sympathetic to a posterior root ganglion. Here, in some way the sympathetic impulse is turned into stimulation of certain spinal ganglion cells which cause the patient to feel pain. This pain he seems to feel in the sensory distribution of the nerve root in question. It is therefore called referred pain. On the basis of this theory, it should have been sufficient to remove the middle and inferior cervical and stellate ganglia on both sides. This of course interrupts all sympathetic connection between cardiac plexus and central nervous system. Consequently, this was done on both sides at the same operation, leaving in place both superior cervical ganglia. It is evident that each superior sympathetic ganglion is now isolated (Fig. 3). Its only connection with the spinal cord which had been by means of the sympathetic chain has now been removed. The superior ganglion is provided only with efferent outlets to the vessels of the brain, the outgoing branches of the fifth nerve, the peripheral distribution of the highest three or four cervical spinal nerves and the cardiac plexus. It cannot be the path for sensory conduction because, first, there are apparently no sensory fibers in the superior cardiac nerve and secondly, because the ganglion now has no known connection with the central nervous system.

Nevertheless, on the ninth day after operation the patient sent for the intern on the ward because of pain in his head and the following is Dr. Samuel Lambert's careful note made at the time:

"The patient was sitting straight up in bed. His forehead was moist with perspiration equally on both sides. The rest of his body was warm but not moist. He was perfectly clear mentally. He said he had a dull pain which started all around his neck, just below his

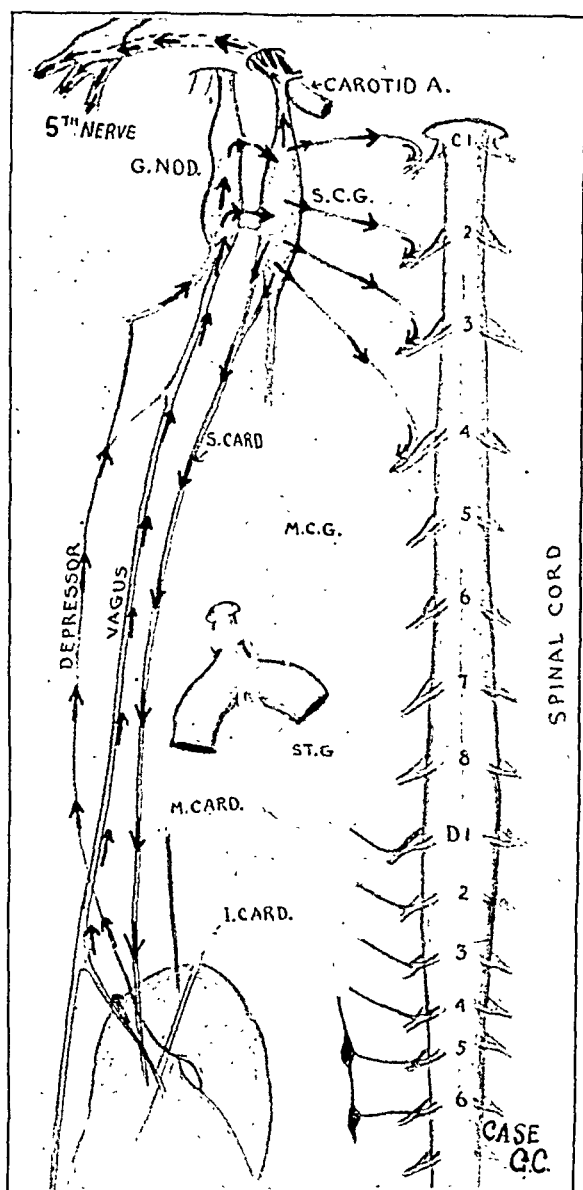


FIG. 3.—Case G. C., middle and inferior cervical and upper thoracic ganglia removed. Arrows indicate direction of impulses in remaining fibers of autonomic system.

jaw, like a collar. It went up into his gums and then up the sides of his head to the top. At the same time he had a feeling of tightness in exactly the same locations. He had no pain or feeling of constriction any other place. His blood pressure was over 300 (systolic) and 0 (diastolic). He felt a little nauseated momentarily.

"He was given 0.0006 gm. nitroglycerin. After five minutes he said the pain had entirely left. In the patient's words, 'It just kind of floated away.' His blood pressure was still 300 (systolic and 0 (diastolic).

"Fifteen minutes later he said he had a very slight pain returning in his lower jaw. The blood pressure was still 300+ and 0. There was no perspiration on his forehead. The pulse throughout 82 to 86.

"One-half hour later he was given a second dose of nitroglycerin and the pain was completely gone. The blood pressure was 170 (systolic) and 0 (diastolic)."

It is now a little over a year since the operation and although he was restored to activity again, he has continued to have attacks of angina pectoris in the face, head and sometimes neck. These attacks are easily relieved by nitroglycerin.

It is impossible to explain these seizures on the basis of referred pain. The angina which the patient experienced was in the distribution of the fibers of the superior sympathetic ganglion which accompany the branches of the fifth nerve and upper three cervical nerves, but this ganglion is cut off from the central nervous system. Therefore, I have assumed that the ganglion is stimulated by a reflex in the autonomic system.

Similar reflexes have been described in the sympathetic nervous system elsewhere, and called by Langley and Anderson¹⁰ axone reflexes (Sokownin reflexes). Simply expressed, they may be described as follows: Axones (in the lumbosacral autonomic) as they pass on down a nerve, such as the hypogastric, send off connector fibers to numerous cells in the adjacent sympathetic ganglion. Stimulation of the axone below awakens to action the motor cells in the ganglion which receive connectors from that axone. Thus if the inferior mesenteric ganglia be isolated from the central nervous system and the right hypogastric nerve be cut and its upper segment stimulated there results blanching of the bladder and rectum on the other side. These long axones which give rise to axone reflexes were shown to have their nerve cells in the central nervous system. Gaskell, in his masterly book on "The Involuntary Nervous System," after discussing these splanchnic reflexes, says, "There is no reason to suppose that one part of the involuntary nervous system differs in essentials from another. I imagine, therefore, that the cranial connector fibers in the vagus nerve . . . also send off collaterals so as to connect with more than one motor nerve cell; that therefore, when the organs supplied by such motor cells are isolated from the central nervous system, reflexes can take place in them which are also of the nature of axone reflexes."

Therefore, in the opinion of Gaskell, it would not be contrary to what is known of the physiology of the involuntary nervous system to suppose the vagus may enter into an axone reflex. If one assumes that stimulation passes from the irritable area in the heart or

aorta by way of the vagus or depressor nerve, it would then be transmitted by connector fibers through the abundant anastomosis from the ganglion nodosum to the ganglion cells of the superior sympathetic. These motor cells being stimulated would cause spasm in the bloodvessels innervated by that outflow, that is, the coronary arteries, the vessels of the head, face and neck. Their activity would likewise cause sweating in the same peripheral area (and this was the case), and the constriction of the vessels might perhaps be expected to raise the blood pressure still higher, a condition which also was found true.

If it is the actual peripheral arterial spasm that is responsible for the sensation, the use of a drug which relaxes the smooth muscle of these contracting vessels should abolish the pain, independent of the drug's action on the heart. Of course the specific physiological action of nitrites is to relax smooth muscle. It may be thus that it relieves angina pectoris.

I have used the word pain to describe the sensation of angina, but this patient, like many others, describes it as a pressure or great weight, something like a terrible constriction. This characterized the sensation as felt formerly in the precordium and arms and, since the operation, in the face.

If the immediate cause of the angina is peripheral vessel spasm, this spasm must be felt directly by the patient, through the same cerebrospinal paths used for the conduction of ordinary types of pain, as is the case in certain other sympathetic reflexes to be mentioned below.

The second patient to be described S. A., aged thirty-eight years, had a general arteriosclerosis and hypertension, his blood pressure averaging about 210/105. Walking across the ward was sufficient exertion to precipitate a severe attack of angina pectoris, felt as pressure in the precordium and left arm.

I removed the left cervical sympathetic chain, including all the cervical ganglia and the stellate ganglion, on the advice of Dr. Levy. When the patient became active after the operation, typical attacks of angina pectoris reappeared. But now it was on the right side and the sweating which accompanied it was on the right side of the face and right arm. Some pressure was felt in the upper sternum, right side of the neck and inner aspect of the right arm. These attacks continued and he was again operated upon. This time, because of the good results reported by Coffey and Brown, the simple operation of removing the superior sympathetic ganglion was performed. On the third day after removal of the right superior ganglion, angina recurred. Now the pain appeared to be in the right arm, the right neck being left out, and sweating now during attacks was altogether absent in the face but appeared in the right arm and chest.

Thus a third time we see that the angina was felt in the area where

the sympathetic motor supply was intact. After the second operation the patient's systolic pressure fell from an average of 210 to 170. It rose, however, as was the case with the first patient, during attacks (reaching 205). Recovery from the immediate effects of the operation was satisfactory, but on the eighth day after operation the

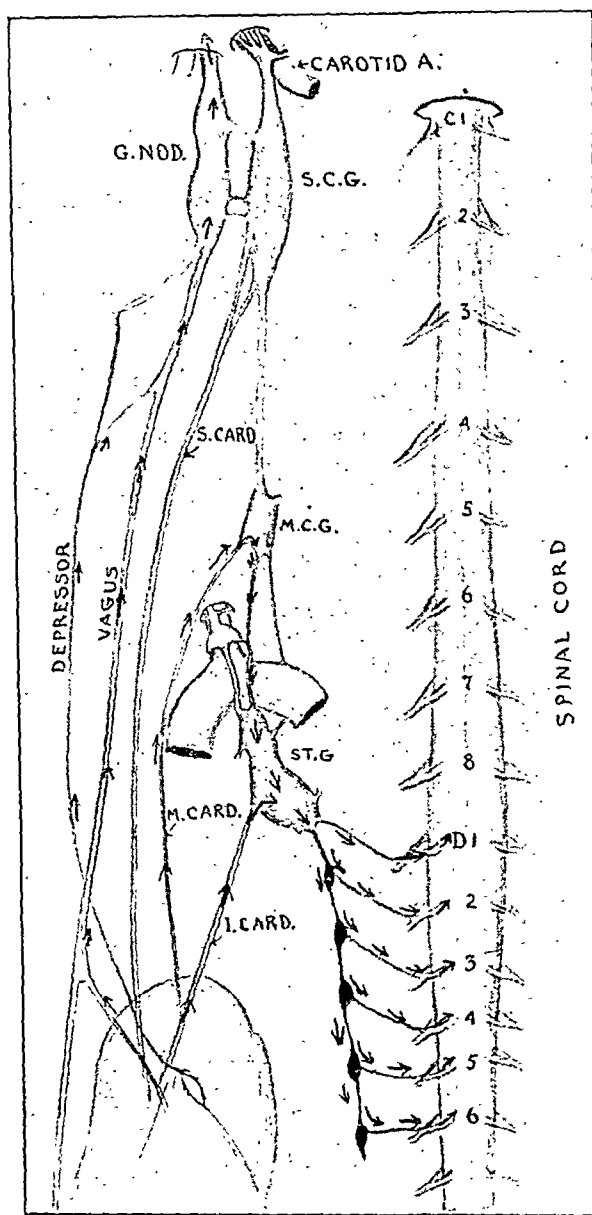


FIG. 4.—Case S. A. (right side). Superior sympathetic ganglion has been removed. Arrows indicate direction of impulses in remaining fibers.

patient suddenly had what Dr. Levy thought was a coronary occlusion, and he died on the sixteenth day.

As seen in Fig. 4, the second patient presented on the right side a condition the reverse of that which obtained in the first patient. The mechanism is present for a possible explanation of the angina

on the basis of Head's theory of referred pain. That is, there are present afferent paths from cardiac plexus to the upper thoracic spinal cord. On the other hand, before the superior ganglion was removed, some of the discomfort was felt in the right neck, an area supplied with motor fibers from this ganglion. After the removal this pain was not felt.

On the theory of an axone reflex, the conditions are exactly the same as those in which these reflexes occur elsewhere in the sympathetic nervous system. By stimulation of sympathetic axones in the cardiac plexus, the motor cells in the intact sympathetic ganglia would be excited causing localized sweating, arterial spasm and some increase in blood pressure.

On the above theoretical basis certain phenomena of angina are easily explained. Mackenzie,¹² when investigating the pilomotor (or goose skin) reflex, found that rubbing lightly the skin under the left breast caused the goose skin to pass up the left side of the chest and down the inner aspect of the left arm. This sympathetic reflex induced a chilly sensation in the same distribution. When he tried the reflex on a case of angina, the patient remarked in surprise that the chilliness corresponded with the usual distribution of his pain. This pilomotor reflex is due to a sympathetic motor discharge and the resultant sensation of chilliness is reported to the consciousness by way of the sensory spinal nerves. The mechanism is the same as has been suggested above for angina and the resulting sensation has the same peripheral distribution.

The hyperesthesia which may follow a seizure would indicate that the pain was due to a peripheral condition, just as any severe pain from a peripheral cause may leave a hyperesthesia of the skin. Patients at times complain that pressure on some area of skin which may be quite small and well localized induces a bout of angina. Such pressure might perhaps set up smooth muscle contraction in an area already receiving subliminal stimulation.

That an angiospasm originating in the stellate ganglion may be the cause of the pain in angina was suggested also by Brünning² for the following reasons: (a) In handling the ganglion preparatory to removing it he observed that his patient's left arm became suddenly blue as in Raynaud's disease; (b) the fact that blood pressure rises during attacks.

The new hypothesis proposed for the explanation of the nervous mechanism in angina pectoris depends upon an autonomic reflex. It might well be called, therefore, *reflex pain*. It causes peripheral spasm of smooth muscle and thus may resemble the pain in various angiospastic conditions. It differs from the referred pain of Head principally in that the point of contact of sympathetic and cerebrospinal system is shifted from the posterior root to the periphery where there are other analogous contacts between the two systems. No attempt is made in this communication to expand the hypothesis

to other types of visceral pain nor to analyze different kinds of cardiac pain.

Conclusions. The following practical conclusions may be drawn:

1. The removal of a sympathetic ganglion removes the possibility of angina pectoris in the *motor* distribution of that ganglion only.

2. Pain is still possible in the motor distribution of the remaining ganglia, provided the stimulus arising in the heart or aorta is adequate.

3. Success in the operation depends not upon interrupting a direct afferent path from cardiac plexus to central nervous system as has been assumed, but upon the interruption of autonomic reflexes.

4. Complete cervico-upper-thoracic sympathectomy abolishes the pain, but should only be employed in cases where life is really insupportable even under the best medical care.

5. Removal of the superior cervical sympathetic ganglion does not render angina in the motor distribution of the other ganglia impossible. Its removal can only be justified on the basis of some resultant alteration in the coronary vessels or aorta which are innervated by it through the superior cardiac nerve.

6. Even if the operation is successful in abolishing pain, the patient should not be called cured but should still be considered as having a serious cardiac disease, and be treated accordingly.

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LIPIODOL IN NEUROSURGERY.

WITH A REPORT OF A CASE WITH DELETERIOUS RESULTS.

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EVER since neurosurgery has entered into its important sphere as a specialized entity, neurosurgeons as well as neurologists have been seeking to overcome the errors encountered in false spinal localization, especially in reference to the diagnosis of spinal cord tumors, and have been searching for some method whereby the exact level of cord obstruction could be accurately determined. It is not an unusual occurrence for neurosurgeons to explore a vertebral canal at a site much lower than where the true lesion actually is located.

The best indicator at our command at the present time for disclosing a level lesion is a careful and thorough neurologic examination; but even the best present-day study is at times not sufficiently accurate. The Ayer¹ test is of inestimable value in the differential diagnosis of spinal subarachnoid occlusion, and yet it lacks the all-essential and much-desired faculty of localization. The Queckenstedt² test also is not infallible in its results: In cases of incomplete or partial spinal obstruction the interpretation of the findings obtained from this procedure often leaves us in a dilemma. I personally have always regarded this test merely in the light of a confirmatory observation and have not considered it as a decisive indication; nor have I permitted normal readings to sway me from the diagnosis of cord compression when the neurologic findings indicated such a lesion. The same objection can be raised to this sign as to the Ayer test, namely, it fails to localize the segment. Dandy's³ method of introducing air into the spinal canal appears to be the nearest approach to a satisfactory solution of the problem, aside from being entirely harmless. In the cervical region one is apt to become confused with the air in the trachea, but in the other regions of the vertebral canal the level of air is more distinct and less apt to cause confusion.

In 1921 Sicard and Forestier⁴ first reported the value of lipiodol as a means of determining the absolute localization of spinal subarachnoid blockage. Lipiodol is a 54 per cent solution of metallic iodine in a vegetable oil. This substance is introduced into the vertebral canal by way of a puncture of the cisterna magna and the oil permitted to gravitate down to the site of the spinal obstruction where it remains impinged. A Roentgen ray photograph is then taken to reveal the opaque substance at the exact site of occlusion. In October, 1923, Sicard, Paraf and Laplane⁵ reported the

intraspinal use of lipiodol in 150 cases, of which 50 were given by the way of the cisternal route, without any fatalities. The impression gained from these authors is that this material is a perfectly harmless and innocent solution, in spite of the fact that it is almost nonabsorbable and has remained *in situ* for over two years in some of their cases. Sargent⁶ has corroborated the visualizing and localizing value of this preparation in 3 cases which at operation revealed three spinal cord tumors.

Ayer and Mixter,⁷ experimenting with iodipin,* a less irritating preparation, and also with an iodine preparation of the same percentage as the original French product, found that the six cats employed in their work displayed evidences of meningeal irritation. The cell count in the spinal fluid of 1 case was 2700 cells per c.mm. the day after the injection of the oily preparation and 4420 in another case on the third day after the injection. One cat died of convulsions. These workers next injected iodipin into the subarachnoid spaces of 2 patients, and they felt that in 1 case a reaction was displayed by an otherwise unexplained rise in temperature for one week. They concluded that the oily substance (iodipin) was distinctly irritating and its use should be greatly restricted and guarded.

My experience with lipiodol has been limited to 3 cases, 2 of which I have not been able to follow up and the other case, the cause of this report, has demonstrated to me unequivocal and undoubted evidence of the irritative power of this substance.

Case History. Mr. V. L. (N. Y. P. H., No. 4914), aged thirty-seven years, married, white, laborer, born in Finland, was admitted for the first time on May 5, 1924. The patient entered the hospital with the complaint of difficulty in locomotion for the past two and one-half years.

About four and one-half years previously the patient first noticed that his left leg felt numb and that it soon became anesthetic to both heat and cold. This was readily noted on immersing the lower extremities into water and has persisted up to the present. His right leg remained normal. Two years later weakness in the right knee occurred with a slight limp on that side. After an interval of six months he began to drag the right foot. One year later involvement of the left leg began with stiffness. Both legs have grown progressively worse and have increasingly incapacitated him in his locomotion. The legs are easily fatigued by walking, which is not felt when he is either sitting or reclining. At no time during the course of his entire illness were there any symptoms referable to the involvement of the rectal or vesical sphincters. Venereal diseases were emphatically denied.

* Iodipin, 40 per cent solution of iodine in a vegetable oil, prepared by Merck & Co.

At the age of eighteen years the patient, while employed as a seaman, fell 15 feet into the hold of a ship. He was unconscious for two weeks. At this time he sustained a cranial as well as a vertebral injury. He was discharged from the hospital in three months without any residual paralysis.

Physical Examination. The gait was that of a typical spastic paraplegic; all associated movements were normally present. A slight Romberg sign was noted. There was also a fine rapid tremor of the hands. Ataxia and adiadochokinesis of the upper extremities were absent. The motor system indicated definite and severe involvement. The deep reflexes of the upper extremities, such as the biceps and triceps, were equally active; the patella reflexes were equally markedly exaggerated; percussion of the tendo Achilles produced transient clonus on both sides; persistent and permanent clonus was elicited at both tendo Achilles; double Babinski and double Chaddock signs were obtained. The four superficial abdominal reflexes were all absent; the cremasterics on the other hand were both normally present.

The cranial nerves were practically negative. The right fundus showed a distinct pallor of the temporal rim of the disc; on the left side the physiologic cup was very distinct, and there was less suspicion of a temporal pallor, although there seemed to be some slight indication of the same. The pupils were equal and reacted to light; accommodation and consensual reflexes. The extraocular movements were normal. A slight bilateral nystagmus was observed which was more marked on looking to the right and became less on persistently looking to the same side. The corneal reflexes were active and the sensory as well as the motor supply of the trigeminal nerves were normal. The facial reflexes on both sides were intact. The Rinne's tests were positive; the Weber test on the right side responded normally; on the left the test was not correctly interpreted; the greater intensity was referred to the opposite ear on one occasion and of equal intensity in both ears on another occasion. The uvula pointed in the center and moved properly; the pharyngeal reflex was active; the tongue protruded in the center; the movements were normal and no tremor was observed.

The sensory examination revealed a definite level of disturbance in all four tests. To cotton (touch) there was an area of anesthesia extending from the distribution of the fourth lumbar segment to and including the fifth sacral segment on the left side; from the level of the eighth dorsal segment to the fourth lumbar on the same side hypesthesia was present. The right side presented no abnormalities. On testing for pain it was found that hypalgesia extended from the ninth thoracic level down on the left side. The right was again uninvolved. Hot and cold sensations gave the same results, namely, thermoanesthesia from the twelfth dorsal segment down and hypthermoanesthesia from the ninth to the twelfth dorsal

distributions. As with the other tests, the left side alone was affected.

The general physical examination was negative with the following two exceptions, a linear cranial defect in the right frontal bone, 1 inch wide and 5 or 6 inches long, and a kyphosis of the vertebral column at the fourth thoracic vertebra. The cranial defect pulsed and was due to the result of the injury sustained nineteen years previously, as was the vertebral deformity.

Lumbar puncture showed the intradural pressure to be 14 mm. Hg, with clear spinal fluid which did not clot on standing. This specimen contained 2 cells, no globulin and the Wassermann test was negative. A cisterna magna puncture was performed with the intention of introducing lipiodol into the spinal canal to verify the level of compression obtained by the neurologic examination. The intracisternal pressure registered on spinal mercurial manometer was 10 mm. Hg. The fluid was clear. Ten cubic centimeters of fluid was removed and 1 cc. of lipiodol was injected. The lipiodol employed was the same material as used by Sicard and imported from France. Roentgen rays were then taken. The following day another lumbar puncture was performed and a few cubic centimeters of spinal fluid under 14 mm. Hg of pressure were removed. One cubic centimeter of lipiodol was introduced at the lumbar site and the patient turned with his buttocks elevated and his head more dependent so that the oil could gravitate down to the site of the obstruction; Roentgen rays were taken in this position. The Roentgen rays were reported to show the opaque material opposite the seventh, eighth and tenth dorsal vertebrae. This localization did not correspond with the clinical diagnostic level which was the eighth dorsal segment and would be opposite the sixth thoracic vertebra. The difference was so small that it was felt to be confirmatory evidence of spinal obstruction and compression. Operation was advised. The patient left the hospital and was readmitted for operation on May 13, 1924.

On readmission the only change that was noted was in reference to the sensory level. The pain level corresponded to the eighth dorsal vertebra, that is, the eleventh thoracic segment. The pre-operative diagnosis was compression fracture of the fourth dorsal vertebra with meningomyelitic adhesions extending from the eighth to the eleventh dorsal segments.

At operation an incision was made extending from the third to the eighth dorsal vertebra, the muscles retracted and the vertebrae exposed. The spinous processes and laminae of the third, fourth, fifth and sixth thoracic vertebrae were removed and the dura exposed. The fifth and sixth dorsal vertebrae were found fused. The dura was incised, and at the fourth dorsal vertebra, the site of the kyphosis, the spinal cord was somewhat kinked at that point. Both the dura and the arachnoid were very much thickened. No adhesions

were found and the compression was felt to have been caused by the kyphosis of the fourth dorsal vertebra, together with the fusion of the fifth and sixth thoracic vertebræ, and the flexion of the spinal cord at that point. The dura was left unsutured in the closure of the wound. A spinal decompression was really performed. The patient left the hospital on May 27, 1924, two weeks after admission. The postoperative diagnosis was compression fracture of the fourth dorsal vertebra, fusion of the fifth and sixth dorsal vertebræ and an incomplete transverse myelitis of the cord together with some chronic posttraumatic arachnoiditis.

On October 8, 1924, the patient was readmitted to the hospital in a markedly worse condition. His complaint was that his legs "shook," by which he meant that his legs would voluntarily enter into clonus; besides the spasticity had so increased that it was very difficult for him to walk with even the aid of canes. The lower part of the back was beginning to give paresthetic symptoms.

The neurologic examination at this time was as follows: The upper deep reflexes were active and equal; the lower ones, markedly exaggerated and pathologic. The patellar and suprapatellar reflexes were very active. The Achilles reflex entered into permanent clonus on the slightest percussion; the Babinski, Chaddock and Oppenheim reflexes were present on both sides, the Gordon reflex only on the left and the Hoffmann reflex only suspiciously on the left. The superficial abdominal reflexes were all absent, the cremasterics present on both sides. The cranial nerves were negative in the main, with very slight exception, namely, a possible slight paleness of the temporal side of the right disc; the fundal vessels and pathologic cup were normal, and a bilateral nystagmoid movement, more marked on looking to the right, was observed. The sensory examination revealed multiple, patchy areas of disturbances, grading from complete anesthesia into marked hypalgesia and hypesthesia. These findings were more marked on the left side and extended from the eighth or ninth thoracic segment down. Ataxia, adiadochokinesis and tremor of the upper extremities were absent. This patchy distribution of the sensory changes together with an ill-defined level brought the possible diagnosis of multiple sclerosis into serious consideration. A Roentgen ray of the spine showed a portion of the opaque material (lipiodol), which was introduced into the spinal canal on May 7, 1924 (five months previously), lying opposite the seventh, eighth and tenth thoracic vertebræ. The patient was discharged on October 10, 1924, with the diagnosis resting between multiple sclerosis of the spinal form and spinal leptomeningeal adhesions extending from the eighth to the tenth dorsal levels together with the presence of the foreign body lipiodol.

The patient was readmitted for operation on October 22, 1924. He was subjected to another laminectomy on October 24, 1924. The spinous processes and laminae of the seventh, eighth and ninth

thoracic vertebræ were removed; the dura incised and joined to the incision made at the previous operation. Dense recent leptomeningeal as well as meningomyelitis adhesions were found; the arachnoid was very much thickened and there was no question but that the damage to the tissues noted at this operation had been produced since the last exposure of the canal. Two arachnoidal cysts, one the size of a green pea and the other the size of a kidney bean, lying opposite the eighth and tenth dorsal segments contained lipiodol; these were incised and the oil liberated. It was felt that these encysted masses, aside from producing spinal-cord compression, had recently caused an inflammatory process which resulted in the new lesions noted above. The dura was again left open and the muscles and fascia closed over it. The patient was discharged, December 18, 1924, without any improvement resulting from the operation. He was seen several times later, but improvement had not occurred; in fact, it appeared as if he were growing progressively worse.

Comment. This case demonstrates beyond a doubt that the only possible factor responsible for the increase in the intraspinal condition, which was plainly visible to the naked eye, must be attributed to the irritative action of the lipiodol. At the time of the first operation the dense adhesions between the leptomeninges and the spinal cord and the advanced picture of the arachnoid thickening which were found at the second exposure were absolutely lacking. The pathologic state was altered to a severe extent within a period of five months which was the duration of the lipiodol encystment in the subarachnoid space. It was obviously evident that the progression in the clinical manifestations could be unbiasedly and solely laid to the action of the lipiodol.

The obnoxious result obtained in this one case sufficed for me to abandon the use of this substance in all future instances. I much prefer to rely upon my neurologic findings for localization without the assistance of any such possible drastic measures. It is a horrible experience that one does not wish to witness more than once in his practice, if at all.

Any substance that may remain in the subarachnoid space for years must, if unremoved, produce at least enough tissue reaction to become walled off. This amount of reaction in this situation is sufficiently deleterious to warrant the use of lipiodol to be discarded. Nerve tissue, one must remember, does not regenerate once it is destroyed. All central nervous tissue destruction is permanent and inflammatory processes here produce permanent damage.

To assume that reactions may not occur from the lipiodol, one need only recollect that all foreign bodies lodged in the human body, regardless of the situation, tend to produce a protective fibrous capsule and thereby become encysted. The case reported has given me enough vivid evidence that nerve tissue reacts in

the same general manner as all other tissues, at least in respect to foreign bodies. It is difficult to conceive that a substance composed of such a high percentage of iodine should not have some irritative effect upon such delicate structures as the spinal cord with its coverings.

Aside from Ayer and Mixer,⁷ who also advise against the indiscriminate use of lipiodol or iodipin, I am not aware of any other authors who have published cases with harmful results. This reported case is the only one I have knowledge of where the actual tissue changes before and after the use of lipiodol were visually observed and recorded. It may be possible that this particular individual's condition was one where lipiodol was contraindicated in that the original injury was fertile soil and was conducive to the formation of adhesions upon the slightest provocation.

I feel that lipiodol should be employed only as a last resort, and should be entirely restricted to those cases where laminectomy is to be performed within a few days, at which time the oil can be liberated from the canal. No doubt that the several authors who reported the successful use of lipiodol as a localizing agent in spinal-cord neoplasms removed the oil at the time of the operation, and therefore none of the possible irritative effects were obtained.

Conclusions. 1. Lipiodol—a 54 per cent solution of metallic iodine in a vegetable oil—is almost nonabsorbable.

2. One case is reported wherein the intraspinal damage was definitely increased, owing to the use of lipiodol.

3. Lipiodol can be said to be irritating if left within the subarachnoid space over an indefinite period of time.

4. It is advisable not to employ this new material as a means of localization, except as a last resort and only if laminectomy is to follow within a few days. The oil should then be removed from the intradural space.

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ACUTE TYPHOID CHOLECYSTITIS FORTY-ONE YEARS
AFTER ORIGINAL INFECTION.

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WE recently observed a patient operated upon for acute cholecystitis without calculi. *Bacillus typhosus* was obtained in pure culture from the gall bladder. There was a definite history of typhoid fever forty-one years before operation with no symptoms suggestive of gall bladder trouble in the interim.

In reading the available literature we were particularly interested in the following general statements: Osler and McCrae¹ say that typhoid bacilli have been found in the gall bladder of patients who never had typhoid fever. Cholesterol gall stones containing typhoid bacilli have been observed to form, apparently within sixty-eight days of the onset of typhoid fever.² "Some hundreds" of cases of typhoid fever were traced to a milk supply from a farm looked after by a typhoid carrier who had had typhoid fever forty-seven years before.³ Garbat⁴ made observations on typhoid convalescents, making cultures from the stools and from the bile obtained by duodenal tube. Of 136 cases thus studied, the bile from 15 per cent still showed typhoid bacilli when 3 consecutive cultures from the stools had been negative.

The following definite statements were made as to the intervals after typhoid fever at which the bacilli were actually recovered from the gall bladder or from gall stones. In *Modern Medicine*⁵ it is said that the bacilli may persist in the gall bladder after an attack of typhoid fever for an indefinite period, instances of fourteen, seventeen, and eighteen years being cited. Dowd⁶ has reported a case of cholelithiasis in which living typhoid bacilli were found in the gall stones thirty-two years after typhoid fever. Clairmont⁷ has reported a case of cholecystitis in which typhoid bacilli were recovered from the gall bladder thirty-eight years after an attack of typhoid fever. He does not state definitely whether calculi were present. This is the longest interval, between the time of the original disease and the recovery of the organisms from the gall bladder, of which we can find a record.

Kehr⁸ advised cholecystectomy and drainage of the hepatic duct by a *T* tube in patients known to be typhoid carriers at the time of operation. The drainage tube was kept in place until typhoid bacilli were no longer present in the discharge. He reported 10 cases operated upon in this manner with a successful result in 8.

The history of our case is as follows:

On October 10, 1924, G. C., business executive, aged fifty-seven years, entered Lakeside Hospital complaining of abdominal pain. The pain and nausea had commenced two days before while the patient was in New York City, and were thought to be due to some melon that he had eaten. A diagnosis of indigestion was made, and castor oil prescribed. However, the symptoms persisted and were somewhat aggravated by a railroad journey to Cleveland. The pain was greatest in the upper right abdomen, but it radiated to the back and right shoulder.

The past history was negative with the exception of typhoid fever forty-one years ago. This was a typical case with several intestinal hemorrhages. There can be no doubt as to the clinical diagnosis forty-one years ago, for the patient was attended by the father of one of the authors (L. A. P.), who was accustomed to refer to this illness as an extremely severe case of typhoid fever. After this attack the patient had no symptoms suggestive of gall bladder trouble until the onset of the present illness.

Physical examination showed marked tenderness and muscle spasm over the gall bladder region with the gall bladder palpable as a tender mass. There was no jaundice. Otherwise the examination was negative except for a heart of normal size with no murmurs, but a pulse grossly irregular as to rate, rhythm and volume. The temperature was 38.5°. The blood pressure was 136 systolic and 78 diastolic. The leukocyte count was 12,000.

A diagnosis of acute cholecystitis was made and operation advised.

Operation was performed soon after the admission of the patient to the hospital. A 10-cm. incision through the upper portion of the right rectus muscle revealed an acutely inflamed gall bladder. A few adhesions to neighboring organs were broken up. Aspiration of the gall bladder showed a mixture of pus and bile. No stones were found in the gall bladder or in the ducts. Because of the condition of the patient's circulation it was considered safer to drain the gall bladder than to remove it. A drainage tube was sutured into the gall bladder and an additional cigarette drain was inserted. The remainder of the wound was closed with tier sutures.

The postoperative course was uneventful, the patient leaving the hospital on November 12, with a slight amount of bile still discharging from the wound.

The following is a summary of the bacteriologic examinations made during his stay in the hospital:

October 10. (Day of operation.) Culture made from gall bladder showed *Bacillus typhosus* in pure culture.

October 14. Culture from drained bile showed *B. typhosus* in pure culture.

October 14. Culture from urine showed no growth.

October 14. Cultures from feces showed *B. coli communis*, being negative for *B. typhosus*.

October 17. Culture from blood showed no growth in forty-eight hours.

October 17. Widal test showed no agglutination for *B. typhosus* or for *B. paratyphosus*, α or β .

October 23. Culture from drained bile showed *B. typhosus* in pure culture.

October 23. Culture from bile in drainage bottle showed *B. typhosus* and *B. coli communis*.

October 30. Culture from draining sinus showed *B. typhosus* in pure culture.

November 12. Culture from feces showed no *B. typhosus*.

The technic followed in demonstrating this organism as *B. typhosus* was carried out in the pathological laboratory of Lakeside Hospital. The original culture was made in ordinary nutrient bouillon and subcultures on the Conradi-Drigalski plate medium and also in the carbohydrate serum-water media, according to the method outlined by Hiss and Zinsser.⁹

On December 20, the patient was seen at his home. A culture from the sinus, which still discharged slightly at intervals, and also a specimen of stool were sent to the bacteriological laboratory of the City of Cleveland Heights. The laboratory reported *B. typhosus* in the culture from the sinus but not in the stool.

Conclusions. Our case shows a longer interval between the original attack of typhoid fever and the recovery of *B. typhosus* by culture directly from the gall bladder than any case which we have been able to find recorded.

The fact that the stools of our patient were persistently negative for *B. typhosus*, while the organism was present in the discharge from the cholecystostomy sinus, is of especial interest as corroborating the observations of Garbat⁴ which have already been quoted.

The ideal operation in patients known to be typhoid carriers is a cholecystectomy combined with drainage of the hepatic duct until no typhoid bacilli are present in the discharge.

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THE EFFECT OF ROENTGENOTHERAPY ON THE HUMAN
HEART

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IN a recent experimental study¹ on the effect of direct irradiation on the heart, it was found that no constant or characteristic change occurred in rabbits, when a total dosage comparable to that used in the treatment of human cases was employed. In this study a series of rabbits was radiated at varying intervals, and roentgenograms and electrocardiograms were made frequently to detect any change in the size of the heart or in its mechanism. The hearts were also studied at postmortem. The electrocardiographic studies showed only one rabbit to have any irregularity of the heart action. This occurred immediately following treatment and consisted of a few ventricular extrasystoles. At autopsy a number of the hearts showed a few isolated areas of necrosis and fatty infiltration, but these were not thought to indicate any significant myocardial change caused by the Roentgen ray. They were not unlike the picture of heart muscle during the course of various nutritional disturbances, intoxications and infections. Although this study was considered essentially negative, we thought it might be of value to continue the investigation in human cases because of the increased use of deep radiation over the chest. We were further stimulated by the recent paper of Davis,² who found evidence of considerable myocardial damage in dogs subjected to intense radiation over the heart.

Those patients who were undergoing roentgenotherapy for various neoplasms of the chest offered a favorable opportunity for observing the effect of irradiation on the heart. The plan for study was to take electrocardiograms of a series of patients receiving such treatment over the chest, when the hearts had been exposed to the Roentgen rays. In addition to noting any variations in the mechanism of the heart arising during treatment, frequent clinical examinations were made so as to elicit changes in signs and symptoms referable to the circulation. This investigation also included a pathological study of material collected from the Peter Bent Brigham Hospital and the Collis P. Huntington Memorial Hospital for the purpose of noting histologic changes in the myocardium. The pathologic data was obtained from two groups of patients, those who had received irradiation over the chest, and those who were treated elsewhere over the body. Those who were treated over parts other than the chest were included because of the large total dosage

received and to determine any change in the heart because of the toxic effect of the Roentgen rays.

In referring to the chart, it will be found that 17 cases were studied, 9 by means of the electrocardiogram and clinical examination, and 8 at postmortem. Two of the cases which came to postmortem were examined by us frequently during treatment for any possible changes in symptoms or physical signs, but were not studied by electrocardiogram. The remaining 6 of the autopsied cases were followed at the Huntington Memorial Hospital and their clinical records were available for study.

The electrocardiographic study was entirely negative except in 2 cases (Nos. 9 and 12). The first patient who received the greatest amount of treatment (8225 ma.) of the series showed a slight flattening of the *T* wave in all three leads. Whether or not this has any significance it is impossible to say, because the patient first came under observation after treatment had been instituted, so there was no control electrocardiographic tracing. She developed dyspnea and pain in the chest during the course of therapy, but it is difficult to feel that her symptoms were not entirely due to an extensive carcinoma of the pleura. There were no signs of circulatory failure in this patient. The other case (No. 12) showed various irregularities in the electrocardiograms, such as nodal beats, premature auricular beats, sinoauricular block, premature ventricular beats and interpolated beats. Unfortunately, in this case also no electrocardiogram was obtained before treatment, but at that time the physical examination showed a definitely irregular pulse. This patient, as it will be noted in the chart, received a large total dosage of irradiation, but complained of no symptoms referable to the circulation. The other cases, as mentioned above, were entirely negative by electrocardiogram and physical examination, and they gave no suggestion of cardiac symptoms. The pathological studies showed no evidence of myocardial change, except in the older patients, where there was fatty infiltration, splitting of muscle fibers, fibrosis and so forth; but there was neither hypertrophy nor the histologic picture, as would be expected, of injury produced in the heart muscle.

Discussion. This series is necessarily small because of the difficulty of selecting cases which had received sufficient irradiation over the thorax to justify any final deductions as to the damaging effect on the heart. It was furthermore, impossible to study a larger group at postmortem because the number of suitable cases, both at the Peter Bent Brigham Hospital and the Collis P. Huntington Memorial Hospital, was extremely limited. However, the data, both clinical and pathological, are such that certain deductions may be drawn. In the clinical study there was no symptomatic evidence whatsoever to suggest that irradiation of the chest or elsewhere over the body produced a failure of the circulation, through damage to the myocardium. In those instances where dyspnea and cyanosis developed during the course of treatment the symptoms could be

TABLE—CLINICAL ROENTGENOGRAPHIC AND PATHOLOGIC DATA.

Case No.	Record number.	Age.	Diagnosis.	Region treated.	Total dosage ma. mins.	No. of treatments.	Interval between last observation and treatment.	Electrocardiogram.	Pathological examination of heart.
1	10	Hodgkin's	Chest	945*	2	29 mos.	Negative	Living.
2	21099	64	Cancer of lung	Chest	550*	4	5 days	None obtained	Negative.
3	23117	24	Hodgkin's	Chest	870*	6	7 days	Negative	Living.
4	23877	55	Myelogenous leukemia	Chest	600*	2	1 day	Negative	Living.
5	25702	52	Hodgkin's?	Chest	600*	2	6 days	Negative	Living.
6	22577	61	Multiple myeloma	Chest	720+	3	12 days	None obtained	Negative.
7	24685	38	Cancer of lung	Chest	708+	2	23 days	None obtained	Negative.
8	2584	36	Malignant lymphoma	Chest	3170+	8	8 days	Negative	Living.
9	21163	50	Cancer of breast, metastases	Chest	8225*	8	1 day	(footnote 1)	Living.
10	25866	36	Myelogenous leukemia	Chest	1080*	3	19 days	Negative	Living.
11	23764	48	Cancer of left testicle with metastases	Chest	2400*	4	5 days	Negative	Living.
12	24802	46	Hodgkin's	Chest	1420*	5	4 days	(footnote 2)	Living.
13	231334	45	Multiple myeloma	Lumbar, spine, sacrum	1731+	4	(a) same day (b) 23 days	None obtained	Negative.
14	22806	36	Cancer of pancreas	Upper abdomen	5194+	8	25 mos. 18 days	None obtained	Negative.
15	24392	56	Chronic lymphatic leukemia	Spleen, post, chest	1963+	5	8 mos. 18 days	None obtained	Negative.
16	22992	66	Cancer of uterus	Pelvis, anterior, posterior	1377+	4	9 days	None obtained	Negative.
17	17553	45	Sarcoma mediastinum	Neck	1782+	4	9 days	None obtained	Negative.

* Treated at Peter Bent Brigham Hospital as follows: Target skin dist. = 30 cm. K. V. peak = 140. Filter $\frac{1}{2}$ mm. cu., + 1 thickness sole ether.

+ Treated at Collis P. Huntington Memorial Hospital as follows: Target skin dist. = 80 cm. K. V. peak constant 170. Filter $\frac{1}{2}$ mm. cu.

¹ The electrocardiogram showed a slight flattening of the r wave in all three leads.

² The electrocardiogram showed premature auricular and ventricular beats, sinoauricular block, etc.

There were no changes in symptoms and signs referable to circulation.

explained by the mechanical interference of the tumor on the intrathoracic structures.

The electrocardiographic tracings were entirely negative, except in the 2 cases already cited; 1 which showed an irregularity of the auricular-ventricular complexes and the second a slight variation from the normal in the *T* wave. Neither patient, however, had symptoms referable to the circulation and the one who showed the electrocardiographic irregularity was known to have had an irregular pulse before the beginning of treatment. In the pathologic studies there were evidences of myocardial changes, but they were not unlike those commonly found in hearts of patients advanced in years or in those who had suffered from infections or debilitating diseases. Although the above results are essentially negative, they do not necessarily exclude the occurrence of temporary changes in the myocardium or the possibility of severe or permanent damage following more intensive irradiation. However, if temporary or mild changes were produced, they were unrecognized by methods of clinical examination. It seems therefore, that until more intensive treatments can be given without damage to the skin, there should be no reason to feel that serious injury to the myocardium may be produced through irradiation over the chest.*

Summary. A series of cases irradiated over the chest were studied by means of electrocardiograms and by clinical and pathologic examination for the purpose of determining any changes in the myocardium which could be attributed to the effects of roentgenotherapy. A series of other cases receiving irradiation over parts other than the chest were also studied. There was no definite evidence to suggest that roentgenotherapy in the dosage used was sufficient to cause any temporary or permanent changes in the myocardium which could be recognized by the methods used in this study. When increased dosage can be used without danger of causing skin or systemic reactions the possibility of injuring the heart will need to be reconsidered.

The kind coöperation of Dr. C. L. Brown during the studies at the Peter Bent Brigham Hospital and the assistance of Dr. Raphael Isaacs in obtaining the data from the Collis P. Huntington Memorial Hospital are acknowledged with appreciation.

* Since this paper was sent to the publisher our attention has been called to an abstract in the *Am. Jour. Roent. and Rad. Ther.*, 1925, 14, 289, wherein Schweizer described myocardial degeneration following intensive irradiation of a mediastinal tumor. The amount of treatment was not reported in the abstract, and as yet we have not been able to read the original article (*Strahlentherapie*, 1924, 18, 812).

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A QUANTITATIVE DETERMINATION OF INTESTINAL PUTREFACTION.

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AND

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FOR the past ten years we have been investigating¹ in our laboratory the chemical defence mechanism of the animal as well as of the human body against various foreign organic compounds, particularly against those compounds which might be considered as resulting from abnormal catabolic processes in the body and against various forms of intoxication resulting from the absorption of poisonous substances in cases of so-called autointoxication, intestinal putrefaction, and the like.

In general, there is an initial attempt on the part of the animal organism to oxidize completely or burn up the foreign molecule; if this is unsuccessful there is an attempt at reduction; finally, if both of these methods fail, an attempt is made to conjugate or join the toxic substance to some compound or radicle which seems to reduce the toxicity and at the same time increase the solubility, making possible the rapid elimination of the resulting compound in the urine. Our findings thus far allow us to state definitely that a given species of animal may have a certain definite mechanism of chemical defence against a given substance, while another species of animal may protect itself in an entirely different way. For instance, mammals, including man, protect themselves against ingested benzoic acid by joining or conjugating it with the amino acid glycocoll; but for the detoxication of the next acid in the series, namely, phenylactic acid,² man is the only mammal whose organism conjugates it with the amino acid glutamin. All the lower animals, including the monkey, use glycocoll for this purpose.

We have synthesized in the laboratory many of the products resulting from the putrefaction of protein material in the intestine. With this comparatively large quantity of material to work with, we have been able to study not only the detoxication of the poisonous compounds, but also their physiologic effect upon the body. In general, it may be said that their toxicity is very much less than has been commonly thought, while many of these compounds are absolutely harmless. Most putrefactive products absorbed from the intestine possess both an aromatic nucleus and a side chain; and are not detoxicated by oxidation or reduction but by conjugation. The substances most commonly used for this pur-

pose are four of the amino acids, namely, glycoll, glutamin, ornithin and cystein; also glycuronic acid, acetic acid and sulphuric acid. Others less often employed are the methyl group and the thiocyanate radicle.

One important feature of the detoxication mechanism is that, although these substances used in chemical defence cannot be stored in the body for emergency purposes, they can none the less be synthesized in many cases from refuse material which would ordinarily be excreted in the urine. Sulphuric acid used in this connection is for the most part derived from the catabolism of the animal's own tissues or from endogenous cystein and would otherwise have been excreted as inorganic sulphates in the urine.³ The supply is, therefore, necessarily limited, and cannot be replaced by the feeding of sulphates. A failure of the limited sulphate supply calls forth an apparently unlimited supply of glycuronic acid which seems to be derived from the carbohydrate supply of the body but which, as far as our researches have indicated, may also be derived from the sugar-forming amino acids of protein.⁴ Glycoll and glutamin, two of the amino acids occurring in the protein molecule, may be synthesized by the human body simultaneously for the detoxication of benzoic acid and phenylacetic acid respectively,⁵ even when the subject is maintained on a nonprotein diet or is fasting. The nitrogen necessary for the synthesis of these amino acids is not derived from the breakdown of body tissue, but is taken from the refuse fraction which would have been otherwise excreted in the urine. Benzoic acid is detoxicated by the bird by joining it with ornithin, another amino acid,⁶ which the bird can synthesize for this purpose,⁷ taking the nitrogen from that fraction which would have otherwise formed uric acid, the substance corresponding to urea in mammals. Cystein, the sulphur-containing amino acid, cannot be synthesized by the animal body, but is available for detoxication purposes only when protein containing cystein is ingested.^{8, 9} The validity of these results have been verified by their subsequent *rediscovery* by various investigators,^{10, 11} and authors.¹² The fact that certain amino acids, such as glycoll, glutamin and ornithin, can be synthesized *in vivo*, while others, such as cystein, cannot be built on demand by the body, gives us the much-needed explanation why we have our two nutritional groups of alpha amino acids—the "essential" and the "nonessential."

In more than 13,000 pages of the literature dealing directly with what may be called the chemical side of intestinal putrefaction, the majority of investigators have attempted to determine the extent of bacterial protein decomposition in the intestine by quantitative determinations of urinary indican, or of skatoxyl; others have used the quantitative determination of ethereal sulphates or of glycuronic acid; a few authors maintain that none of these estimations alone gives one an idea of the extent of abnormal amino-acid dis-

integration. They would rely on the ratio of indican to ethereal sulphate as a rough quantitative index of intestinal putrefaction.

While working in this general field we determined to see how nearly quantitatively we could determine these end products of putrefaction after a given quantity of them had been introduced into the gastrointestinal tract of human beings as well as of certain experimental animals. The latter were for the most part rabbits. The human subjects of these experiments were all over twenty-five years of age, and were maintained on a uniform diet; the bowels were regulated as well as possible. The so-called putrefactive products chosen for the experiments were indol and skatol, both of which are derived from the amino acid tryptophan; phenol, derived from either tyrosin or phenylalanin; imidazol, as well as imidazol acetic acid, derived from histidin. The indol and skatol for the human subjects were ingested in small gelatin capsules coated with salicin to insure that the capsule would open in the intestine rather than in the stomach. Each capsule contained 0.05 gm. of the substance. The phenol was simply drunk in a 0.1 per cent solution; imidazol and imidazol acetic acid as dilute aqueous solutions of their soluble hydrochlorids. The rabbits received the water-soluble substances by means of a stomach tube; the skatol and indol, being nearly insoluble in water, were poured down the tube in the form of an emulsion, formed by soaking the substances for some time in warm water and then shaking vigorously. The human urine was collected in twenty-four-hour periods and that of the rabbit in forty-eight-hour periods. On each collection duplicate determinations were made for total nitrogen, urea, ammonia, uric acid, and inorganic, ethereal and reduced sulphur. In addition to these, glycuronic acid was determined in all the urines. On the indol urines determinations were made for free indol and indican (indoxyl potassium sulphate), according to the method of Jolles¹³ as well as the older and better known method of Obermayer.¹⁴ Urines collected after the skatol feedings were examined for skatoxyl potassium sulphate and for skatol, in addition to the regular routine analysis, while the phenol urines were examined especially for phenol. The urines collected after feeding imidazol and imidazol acetic acid were examined quantitatively for imidazol derivatives, according to the test of Koessler and Hanke.¹⁵ As the dosage was relatively small, the feces were neglected. Skatol is perhaps, if anything, more toxic than the indol. Both of these substances caused no distress after 0.05-gm. doses, but after 0.1 gm. there was a distinct feeling of nausea, but no vomiting, followed by loss of appetite, belching and a dull headache which persisted for at least twelve hours after a dose of this size. Phenol had no untoward effects. The imidazol compounds caused a slight but noticeable increase in the pulse rate of 10 to 20 per minute. Two kilogram rabbits were able to receive as much as 0.05 gm. of indol

or skatol without losing their appetite and double this dose of phenol; but as much as 0.1 gm. of indol or skatol caused the animal to remain stupidly in the corner of his cage, showing no inclination toward food but a great desire for water. As much as 0.1 gm. of either imazol or imidazol acetic acid can be fed to a rabbit every three hours without causing more than slight muscular spasms.

TABLE I.—INDOL.

Subject.	Amount fed in mg.	Per cent excreted unchanged.	Per cent excreted as ethereal sulphate.	Per cent excreted as glycuronate.	Per cent excreted as indican (Obermayer's test).	Per cent excreted as indican (Jolles's test).	Total per cent.
Human	50	...	11	...	35	65	11
							35
							65
	50	...	39	...	31	56	39
							31
							56
Rabbit No. 1	100	3	52	12	79	121	67
							79
							121
	50	...	10	...	44	66	10
							44
							66
	80	30	28	...	28	102	58
							28
							102
	100	45	13	...	77	96	58
Rabbit No. 2							77
							96
	150	69	35	...	88	180	104
							88
							180
	200*						
	70	...	33	6	41	75	39
							41
							75
	100	26	74	132	26
							74
							132
	150	78	21	...	122	240	78
							122
							240

* Rabbit died after one hour.

It may be seen from Table I that indol is but slightly detoxicated by combination with sulphuric acid and far less by a combination with glycuronic acid. A considerable amount is excreted free or uncombined whenever the amount ingested exceeds about 50 mg. Since the indoxyl sulphuric acid and the indoxyl glycuronic acid taken together never correspond to the values for indican as obtained by the Obermayer test or the Jolles test, we may conclude either

that the tests for sulphates and glycuronic acid are faulty, or else that indol itself contributes to the indigo formed on oxidation, perhaps through some intermediary reaction as yet not understood. Another point is that the sum of the unchanged indol and the indoxyl potassium sulphate (or indican) and the indol glycuronic acid never equals 100 per cent. Again the figures for indican as obtained by either the Obermayer or the Jolles test are neither consistent nor comparable. We are inclined to believe that the latter test is nevertheless more satisfactory than the older Obermayer test, which invariably carries the oxidation too far, causing a considerable formation of isatin at the expense of the indigo. Besides, in addition to the indigo blue, there is a good deal of indigo red formed; if this is taken into consideration it must be treated first with 10 to 20 per cent sodium hydroxid solution, causing a molecular rearrangement to indigo blue. While Obermayer's test gives consistently low results for indican, Jolles's test gives on the whole results much too high. Our work indicates that glycuronic acid serves only in a minor capacity as detoxicating agent for indol, and is apparently used only after the sulphate supply has been nearly exhausted. The excretion of the glycuronic acid compound, if detected at all, begins usually twelve to eighteen hours after the ingestion of the indol.

TABLE II.—SKATOL.

Subject.	Amount fed in mg.	Per cent. excreted as ethereal sulphate.	Per cent excreted as glycuronate.	Per cent excreted unchanged.	Total per cent.
Human . . .	50	114	..	12	126
	50	82	..	18	100
	150	90	..	32	122
Rabbit . . .	70	66	..	48	114
	100	15	22	33	70
	150	20	..	41	61

It may be seen from Table II that skatol is for the most part detoxicated by conjugation with sulphuric acid and excreted as the ethereal sulphate rather than as a glycuronic acid compound. It is to some extent excreted uncombined, but contrary to the accepted theory, skatol seems to be more easily oxidized to skatoxyl than indol to indoxyl.

TABLE III.—PHENOL.

Subject.	Amount fed in mg.	Per cent excreted as ethereal sulphate.	Per cent excreted as glycuronate.	Per cent excreted unchanged.	Total per cent.
Human . . .	50	18	18
	100	24	22	12	58
	150	22	36	28	86
Rabbit No. 1 .	50	48	..	25	73
	100	33	..	61	94
	150	22	12	79	113
Rabbit No. 2 .	100	36	..	28	64
	150	40	19(?)	56	115
	200	21	..	84	105

Phenol is detoxicated chiefly by joining it with sulphuric acid. The supply of this seems to be derived not only from endogenous catabolism, but also from cystein of exogenous origin, and hence the percentage of phenol detoxicated in this way is dependent on the sulphur-containing protein in the diet. This makes ethereal sulphate determinations a very uncertain indicator of the amount of phenol present.

TABLE IV.—IMIDAZOL.

Subject.	Amount fed in mg.	Per cent excreted unchanged.	Per cent excreted as urea.	Per cent excreted as uric acid.	Per cent excreted as ammonia.	Total per cent.
Human	50	23	23
	100	31	..	3	..	34
	150	33	..	8	..	41
	200	56	..	19	12(?)	87
Rabbit	100	42	42
	150	59	..	12	..	71
	250	66	..	8	..	74
	500	74	..	12	..	86

TABLE V.—IMIDAZOL ACETIC ACID.

Subject.	Amount fed in mg.	Per cent excreted unchanged.	Per cent excreted as urea.	Per cent excreted as uric acid.	Per cent excreted as ammonia.	Total per cent.
Human	50	42	42
	100	68	68
	200	79	..	13	6	99
Rabbit	100	36	36
	200	60	..	6	..	66
	500	81	..	22	..	103

Imidazol and imidazol acetic acid in Tables IV and V were merely estimated colorimetrically. Other work in our laboratory concerning these substances has shown us that the imidazol ring is not oxidized with the formation of a hydroxy compound capable of joining with sulphuric acid and glycuronic acid. On the other hand, it seems to split into uric acid to some extent, and perhaps also into urea and ammonia. Both in the case of the human and the rabbit uric acid seems to be quite a constant derivative from the imidazol ring alone and to a lesser extent from the acetic acid derivative, but the indications are too uncertain to be of value. The test for imidazol itself is quite sensitive but rather elaborate; it is very doubtful whether these histidin derivatives are of sufficient physiologic or pathologic importance to receive so much attention.

It is quite evident that none of our so-called quantitative tests for the best-known putrefactive products in the urine are much more than a rough estimate of the amount of indigo formed in a given quantity of urine by the action of some oxidizing agent like ferric chlorid, and this estimate only a colorimetric one.

At the present time we are attempting to standardize a clinical method for the determination of indol, indoxyl and phenols in the blood, thus giving a first-hand knowledge of any abnormal processes

taking place in the intestine. In addition to this we are taking a number of the ethyl amine derivatives of the alpha amino acids of protein, derived by a splitting of CO_2 from the carboxyl groups of these acids, and we are feeding them to humans as well as to animals to determine their toxicity as well as the course they take in the process of detoxication.

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(LEFT) SHOULDER PAIN OF PHRENIC ORIGIN—A REFLEX SYMPTOM IN CHRONIC APPENDICITIS.

WITH A REPORT OF THREE CASES.

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PHRENIC shoulder pain associated with irritative conditions of the diaphragm is readily recognized, but the association between pain in the left shoulder and a diseased appendix is seldom thought of. Reflex symptoms in chronic appendicitis, according to Rolleston,¹ belong to those complaints which are characterized by hyper-tonus and spasm of the stomach, as well as by failure on the part of the pyloric and ileocecal sphincters to relax.

Spasm of the pylorus associated with chronic appendicitis leads to increased gastric pressure. The accommodating factor for this increased gastric pressure is the gas bubble of the stomach. The mechanism by which the pain is referred to the left shoulder region is brought about by a pylorospasm, increased intragastric pressure, upward pressure upon the left diaphragm by the fornix (fundus) and irritation of the phrenic nerve. The phrenic nerve arises chiefly from the fourth cervical nerve with a filament from the third and a communicating branch from the fifth. Its termination

is in the diaphragm, where some branches are distributed to the thoracic surface and some which pierce the diaphragm are distributed to its under surface. In its origin the phrenic nerve is in communication with the descending branches of the cervical plexus. These branches become cutaneous near the clavicle. Thus we see how pain in the left shoulder region may occur when the left phrenic nerve is irritated as a result of reflex pylorus spasm in chronic appendicitis.

The association between a diseased appendix and pain in the left chest, neck or shoulder region was first called to my attention about four years ago by Dr. Emanuel Libman, during ward rounds at Mt. Sinai Hospital.

Bassler² reports a case of chronic appendicitis simulating angina pectoris in a man aged fifty years, whose symptoms were entirely relieved by appendectomy.

Sir Humphrey Rolleston³ divides the symptoms of chronic appendicitis into four groups—reflex, mechanical, toxic and infective.

In the 3 cases that have come under the writer's observation the symptoms were of reflex origin and were not due to an infection of the phrenic nerve.

Case Reports. CASE I.—W. R. B., a man, aged twenty-eight years, had given a history of having had two previous attacks of appendicitis, at twenty-four and twenty-eight years of age. Each attack was associated with pain and tenderness in the right lower quadrant, vomiting and fever. With rest in bed and local applications of ice the acute symptoms subsided, but the patient continued to complain of heartburn, acid regurgitations and pain in the left shoulder region shortly after meals. This pain would gradually subside between meals to recur again soon after the next meal. He first came under observation, November 3, 1924, complaining of these symptoms and with the history as above stated.

Family History. One brother was operated on for acute appendicitis in 1920. The patient's past history was irrelevant, except for gastrointestinal disturbances such as heartburn, regurgitation of acid secretion and occasional attacks of pain in the right lower quadrant during the past three years associated with constipation.

During the past three months gastric symptoms had become more aggravated. There was a dull pain in the left shoulder region which lasted for about two hours after meals and then gradually subsided. There was also a feeling of distention in the lower abdomen. The appendectomy was advised and performed, and since then the patient has had no further attacks of left shoulder pain and has been free of all symptoms.

CASE II.—J. A. L., a young girl, aged nineteen years, who had her first attack of acute appendicitis in 1921, has been complaining

since then of a feeling of distress in the epigastrium soon after meals with pain in the left chest and shoulder region which was generally relieved by belching. These symptoms persisted for about two years, when a second attack of acute appendicitis brought her to the hospital for an operation. Since then the patient has been free of all symptoms.

CASE III.—H. B., a male, aged twenty-three years, who had been complaining of pain in the left shoulder region with epigastric fullness and heart burn during the past four years. One or the other of his symptoms would usually predominate constantly. There was no history of any acute appendicitis that the patient could remember, although he gave a history of having attacks of stomach-ache as a child.

There was tenderness in the right lower abdomen on all examinations and a Roentgen-ray examination of the gastrointestinal tract showed evidences of a pylorus spasm and an appendix which was fixed, tortuous and filled for a period of one hundred and twenty hours. The appendix was removed three months ago and since then the patient has been free of symptoms.

Held,⁴ in a recent comprehensive article on chronic appendicitis, has properly divided the reflex symptoms into those associated with motor, sensory and secretory phenomena.

1. *Motor Phenomena.* These are evidenced by increased spasm and tonus of the sphincters of the alimentary tract. Moynihan⁵ observed marked gastric contractions and spasm of the pylorus or other parts of the stomach while he was removing a chronically diseased appendix. His term, "appendicular dyspepsia," very correctly designates that syndrome of gastric symptoms associated with appendicular disease. Hurst⁶ observed spasm of the greater curvature during a fluoroscopic examination when he exercised pressure over the area of the diseased appendix. The delay he encountered in the ileum he believed to be due to a spasm of the ileocecal sphincter. Disturbances in motility of the colon with spasm in its various parts is also present and explains the spastic constipation and the pain over the sigmoid area that sometimes occurs. Held calls attention to the fact that chronic appendicitis may at times cause loss of tone in the various parts of the gastrointestinal tract.

In these cases associated gastric atony or the atonic type of constipation may be responsible for a great many of the symptoms encountered. The writer also states that there may occur symptoms of hypertonus and spasm in some parts of the gastrointestinal tract and loss of tone in other parts. It has been the experience of Held that in chronic appendicitis there is often atony of the stomach and spasticity of the cecum or the descending colon.

2. *Sensory Phenomena.* The reflex sensory disturbances manifest themselves by the presence of pain in the epigastric region. Mackenzie⁷ believes that the pain is referred through the sixth and seventh dorsal nerves which terminate in the abdominal walls. Hurst states that the pain is visceral due to hyperperistalsis in the pyloric end of the stomach. Both agree that an irritated focus in the spinal cord is responsible for the increased sensory disturbance obtained by pressure over the skin and muscles in the epigastric area.

If the irritated focus in the spinal cord is in the region of the fourth or fifth dorsal nerves the pain may be thoracic and simulate attacks of stenocardia. If the irritating center is low in the spinal cord pain may radiate down the right thigh or to the urinary bladder. It is well known that when the appendix is situated behind the cecum there may be direct pressure on the ureter with attacks that simulate renal colic. The irritation may even cause red blood cells to appear in the urine. In these cases the symptoms are not reflex but due to direct pressure.

3. *Reflex Secretory Phenomena.* These are evidenced by disturbances in gastric secretion and also by disturbances in the colon. Gastric hypersecretion and hyperacidity are frequently met with, whereas lowered acidity is rare. Attacks of cramps in an associated mucous colitis with discharge of large quantities of mucus occasionally alternating with an attack of serious diarrhea has been reported. Held mentions the fact that frequent urination may be one of the reflex secretory phenomena, but believes that the gastric hyperacidity is responsible for an alkaline urine, thus causing irritation in the urinary bladder and frequency in micturition.

That reflex symptoms vary in different individuals in chronic appendicitis or even in the same individual is often the case. With a depression in the motor function there come a group of symptoms which are entirely different from those associated with a hypertonus of the various sphincters of the gastrointestinal tract. Where the secretory phenomena predominate heartburn, regurgitation of acid secretion or vomiting may occur. It is in this type that the differential diagnosis from gastric or duodenal ulcer is extremely difficult. In a certain number of cases it is known that a chronic appendix may coexist with a duodenal ulcer.

Cope⁸ points out that any condition which may cause irritation of the diaphragm or the contiguous tissues supplied by the phrenic nerve may be the cause of phrenic shoulder pain. It is clear, therefore, that diseases of the liver, stomach, duodenum, pancreas, and so forth, will most commonly cause the pain. He had known the pain to be of diagnostic value in a number of conditions, appendicitis being among them.

He states, however, that it is seldom that phrenic shoulder pain is a symptom in appendicitis, for the very good reason that it is

uncommon for the infection to extend up to the diaphragm. With a long ascending appendix, however, or in the cases where the cecum and the appendix are much higher than normal the symptom is to be expected. The author can only find references to 2 or 3 such cases in the Continental literature, and he himself has known of only 2 cases in which such shoulder pain occurred. He reports a case as follows:

R. M. was taken with acute abdominal pain, followed about fifteen hours later by severe pain over the right acromial region. A perforated retrocecal abscess was found at operation, and there was a great amount of seropurulent fluid in the abdominal cavity. For three weeks after operation slight pain continued to be felt in the right shoulder on deep inspiration. The initial pain in this case was described as that of a nail being driven into the acromioclavicular joint. It is specially to be noted that the pain in this case was not felt on top of the shoulder until some hours after the abdominal pain. This was also exemplified in the second case, in which pain was felt over the right clavicle twelve hours after the onset of the abdominal pain. At operation an inflamed ascending appendix with spreading peritonitis was found, and some lymph was noted in front of the liver.

Orr⁹ states that the shoulder and neck pain, frequently produced in disease involving the diaphragm, is not given its proper importance as a diagnostic aid. The following is a list of conditions in which phrenic shoulder pain or neck pain has been described: Pneumonia, pleurisy, pericarditis, pulmonary infarct, actinomycosis of lower right lung, liver abscess, cholecystitis with peritonitis, perforation of the gallbladder, perisplenitis, appendicitis, ruptured extrauterine pregnancy, pressure of drainage tube and suprarenal tumor. Referred pain to the shoulder or neck is characterized by its spontaneous appearance, and its accurate localization in the distribution of a spinal segment or to a small portion of the segmental sensory distribution, by accompanying hyperesthesia and hyperalgesia and often by increase of pain during deep respiration, cough or change of position. At times the pain is quite severe. In many diseases, especially those in the abdomen, the existence of a shoulder or neck pain is a distinct aid to diagnosis. Its presence is definite evidence that the sensory distribution of the phrenic nerve is involved in the irritation. To be of value, referred shoulder and neck pains must be carefully differentiated from pain due to disease in and about the shoulder. In those diseases having a direct contact with the diaphragm it is quite clear that the pain is referred through the third, fourth or fifth cervical nerves. Shoulder pain in acute appendicitis is rare. To produce such pain it is, of course, necessary for infection to come in contact with the phrenic

nerve. The length and location of the appendix may be factors in this involvement. It is well known how frequently subdiaphragmatic inflammation follows suppurative appendicitis. Evidence of phrenic nerve irritation in such a condition may be of great value. The writer concludes that the diagnostic value of phrenic shoulder pain is definite. When typical it is a positive indication of an irritation to the phrenic nerve and should be sought where disease is suspected in the upper abdomen or lower chest.

In the opinion of the writer of this paper, one should add diseases of the lower abdomen, especially chronic appendicitis, to those that cause phrenic pain in the region of the left shoulder. In the 3 cases reported, there was an associated pylorospasm with increased gastric tension and upward pressure on the left diaphragm which proved to be the cause of the phrenic shoulder pain.

Summary. Three cases are reported in which pain in the left shoulder was associated with chronic appendicitis, acting reflexly through the phrenic nerve, disappearing following appendectomy. The method of production of the pain is discussed.

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REVIEWS.

DISEASES OF THE BRONCHI, LUNGS AND PLEURA. By FREDERICK T. LORD, M.D., Visiting Physician, Massachusetts General Hospital; Instructor in Medicine, Harvard Medical School. Second edition, thoroughly revised, with the addition of a chapter on Pulmonary Tuberculosis. Pp. 776; 110 illustrations. Philadelphia and New York; Lea & Febiger, 1925. Price, \$8.00.

THE physician and the student will find in this work a complete accurate conservative statement of the subject. The thoroughly revised second edition takes full cognizance of recent advances in this field, and of these there have been many. Bronchoscopy has become an invaluable aid to the clinician in the diagnosis and treatment of chronic lung suppuration, foreign body and the various types of tracheal and bronchial stenosis. There have been improvements in Roentgen-ray technic and in thoracic surgery. These are fully appreciated and well presented, as is the newer knowledge of bronchial asthma, of the immunity phenomena of tuberculosis and of the factors underlying recovery and resolution in lobar pneumonia. There has been added in this edition an excellent chapter dealing with pulmonary tuberculosis. A few minor criticisms apply: In regard to the treatment of bronchial asthma, the statement that "The subcutaneous injection of plant pollen, horse-hair protein, or other substances to which the patient is sensitive, is dangerous, and there are no convincing reports in the literature of success by this means," is not wholly in accordance with the facts, especially in the case of pollen asthma. Hereditary telangiectasis is not given among the possible causes of hemoptysis.

R. K.

THE SURGERY OF PULMONARY TUBERCULOSIS. By JOHN ALEXANDER, B.S., M.A., M.D. Pp. 356; 53 illustrations. Philadelphia: Lea & Febiger, 1925. Price, \$4.50.

VERY recently surgery has come to the fore in the treatment of pulmonary tuberculosis of the advanced type, especially in those

cases where other types of treatment have failed to benefit. Surgery today is curing or improving approximately two-thirds of such cases. This work, the first in the English language, presents the entire subject, both for the practitioner and for the surgeon. The detail of diagnosis, and the description of the character of the cases in which surgery should be done, is especially for the edification of the general practitioner. The surgical treatment of pulmonary tuberculosis is one that has been forced upon the American surgeon, as the Continental surgeons have gone further and further away from us in their advances in this direction. The author gives to the reader an up-to-date conception and understanding of the status of affairs today. It is stated in the work that 60 per cent of the patients upon whom radical surgery has been attempted for the amelioration of pulmonary tuberculosis are markedly improved. The work is extremely interesting, as it is new to most of us readers.

E. E.

DISEASES OF THE NOSE, THROAT AND EAR. By WILLIAM LINCOLN BALLENGER, M.D., late Professor of Otology, Rhinology and Laryngology, College of Physicians and Surgeons, University of Illinois. Revised by HOWARD C. BALLENGER, M.D. Fifth edition. Pp. 1080; 569 illustrations. Philadelphia: Lea & Febiger, 1925. Price, \$10.00.

THE fifth edition of the author's *Diseases of the Nose, Throat and Ear* begins with a complete description of the anatomy and physiology of the nose. The obsolete operations of the nasal septum, such as the Gleason, Bosworth, etc., are still described in detail. The submucous resection is beautifully illustrated and easily understood. Most modern methods of treatment, medically and surgically, of the accessory sinuses are given with beautiful illustrations.

The tonsil question is taken up in detail. Indications for local and general anesthesia. Various operations are described, particularly the Sluder, Ballenger's modification and the dissecting method. The larynx is fully considered, from simple laryngitis to total laryngectomy.

The chapter on the ear is systematically and clearly written with beautiful illustrations of the simple and radical mastoid operations and its complications. The physiology and pathology, and the newer operations of the internal ear, are well described and illustrated. At the end is a bibliography and an index. This work is one of the best published to date and is well worth possessing and reading by students, general practitioners and specialists.

D. H.

PREVENTIVE MEDICINE. By MARK F. BOYD, M.D., C.C.H., Member of the Regular Field Staff, International Health Board of the Rockefeller Foundation. Second edition. Pp. 429; 135 illustrations. Philadelphia and London: W. B. Saunders Company, 1925.

THE practitioner or medical student will find in this enlarged edition, a work which amply fills his requirements in the field of preventive medicine, while the teacher of hygiene will appreciate its value as a reference book. The topics range from epidemiology to the hygiene of infancy and from demography to ventilation and exercise. Except for a few chapters which are arranged in rather too tabular a form, the book makes "interesting reading," and certainly contains a vast amount of useful information.

J. A.

PERSONAL AND COMMUNITY HEALTH. By CLAIR ELSMERE TURNER. Pp. 426; 53 illustrations. St. Louis: C. V. Mosby Company, 1925.

THE book presents the facts of healthful living and the scientific principles upon which health practices rest. The public health is considered from the standpoint of what the college and professional man, who is not a sanitarian, needs to know to protect his family and meet his responsibility as a citizen.

Chapters are devoted to various phases of personal hygiene. The science of disease prevention is presented in several chapters. Other chapters deal with food control, water supply and waste disposal. In appendices are given brief explanations of the essential facts in the control of communicable diseases and in the use of disinfectants.

The subject is treated in a logical manner and in convincing style. The book should appeal to that large group of persons who are no longer in college.

D. B.

AN INDEX OF TREATMENT. By VARIOUS WRITERS. Edited by ROBERT HUTCHISON, M.D., F.R.C.P., Physician to the London Hospital and Physicians to the Hospital for Sick Children, Great Ormond Street; and JAMES SHERREN, C.B.E., F.R.C.S., Surgeon to the London Hospital and Consulting Surgeon to the Poplar Hospital for Accidents. Ninth edition, revised and enlarged. Pp. 1035; 108 illustrations. New York: William Wood & Co., 1925.

THIS textbook, now well known in this country, is of real value to the general practitioner for whom it was written. The intro-

ductory chapter on the general principles of treatment by the senior editor is full of common sense and inspires confidence in the great mass of detailed data that follows. Of the ninety-six British contributors some are internationally known and all have good hospital connections. The subjects are alphabetically arranged, quite concisely handled and include most of the medical and surgical conditions commonly encountered in practice. It is surprising, however, to find no mention of pneumoconiosis or spirochetosis icterohemorrhagica and only a single and very inadequate paragraph on the subject of purpura. Furthermore, a tendency to give undue attention to the use of drugs in certain conditions is noted, and a neglect of other more rational procedures. No mention, for instance, is made of transfusion in the treatment of shock, although pituitrin and adrenalin are recommended. On the whole, nevertheless, the book meets a need and the reviewer is glad to have it on his shelf.

T. M.

ARTERIOSCLEROSIS: A SUMMARY VIEW. By the late Rt. Hon. SIR T. CLIFFORD ALLBUTT, P.C., K.C.B., M.A., M.D., F.R.S., etc. Pp. 108; no illustrations. London: Macmillan & Co., 1925.

AN essay in six chapters, enlarged from a postgraduate lecture at Cambridge, this booklet summarizes the author's views on this complex subject. Seen through the press after the death of its distinguished author last February by his successor, Sir Humphrey Rolleston, who contributes a short note, the book substantially repeats the views expressed in the larger work, *Diseases of the Arteries*, which was published in 1915. The first chapter on "Meanings" is especially valuable in defining the field and as an illustration to medical writers of the value of precision in terms and expression.

Many may not be willing to accept the author's view that *hyperpiesia* (to be distinguished from the hyperpiesis of chronic Bright's disease) is a distinct disease, probably due to some "warp in metabolism," which turns out some pressor amine or fails to excrete it. They will find, nevertheless, edification in the impartial presentation of the earlier chapters and practical advice of value in the chapter on Therapeutics. Only one typographical error was observed—"stony" for "atony," on page 41.

A hasty survey of the authorities quoted shows about 100 out of 150 by English authors and only 20 in foreign languages! Such a disproportion, to say the least, emphasizes the handicap placed on scientific internationalism by the curse of tongues.

E. K.

THE MEDICAL FOLLIES. By MORRIS FISHBEIN, M.D., Editor of the *Journal of the American Medical Association*. Pp. 223. New York: Boni & Liveright, 1925.

A CONTINUATION of the American Medical Association's energetically conducted campaign of propaganda against quackeries of all sorts, this book contains most of the strong and weak points of this popular form of human endeavor. Undoubtedly, it is "a book with a wallop," and should appeal to the intelligent and impartial layman when the two are placed in contact. While its influence is thus clearly for good, one cannot but feel that an even stronger impression would be made if a less intolerant attitude were adopted toward those "follies" that are not arrant quackery and knavery, and less emphasis were placed on the powerful organization that the author represents. The inroads of osteopathy and chiropractic may be estimated from the fact that one-quarter of the space is given to these two of the fourteen chapters. In the description of the earlier cults, a calmer historical spirit prevails—as one would expect from the secretary and editor of the Society of Medical History of Chicago—and the final chapter is a strong plea for a rational attitude toward the science of healing. In picturesque description the high point is reached in the excerpts from Andrew Still's autobiographic notes, which take us back to Fifteenth Century Italy in their Cellini-esque style. E. K.

METHODS IN SURGERY. By GLOVER H. COPHER, M.D. Pp. 232. St. Louis: C. V. Mosby Company, 1925.

THE author takes up in detail the routine procedures that have to be performed in the daily life of the average hospital. The book is prepared after the technic and regime used at the Washington University School of Medicine, in the Barnes Hospital and the St. Louis Children's Hospital. He devotes the first chapter to information with regard to history-taking and physical examination in detail. Subsequent chapters take into consideration the running of the various departments of the hospital and the professional interrelationship between the residents, the nurses, the staff and the department officers of the hospital. The pre- and post-operative care and many of the minute surgical procedures are outlined in detail. The book is an excellent one from the standpoint of telling one how to get along in a hospital, and could well be recommended to all students about to undertake a resident or internship at any hospital. Perusal of this little book will prevent many unfortunate, irritating and a few serious mistakes. E. E.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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Uremia and Nephritis.—In this address before the Toronto Academy of Medicine, MEAKINS (*Canadian Med. Assn. J.*, 1925, 15, 771) discusses the functions of the kidney and then very briefly discusses what is uremia. He says very truthfully that we do not know just what is the cause of this condition, which primarily is due to some cellular disturbance. The blood reflects in part this disturbance, but it is certainly doubtful if it does so accurately under abnormal conditions when the blood may be altered by a disturbance of the water balance, a disturbance of the acid-base equilibrium and an alteration of the relative importance of the inorganic constituents of the body fluids. He concludes by asking the questions: "Does the body endeavor to maintain as far as possible the acid-base equilibrium in the arterial blood and in the tissues, and in attempting this does it violate another principle of greater importance; namely, the proper balance of the inorganic constituents of its internal medium? . . . Has the correction of one balance lead to the disturbance of a more important one? And is the explanation of the symptoms of uremia to be found in a combination, in different proportions in different cases of these three important biologic equilibria?"

Syphilis of the Heart and Aorta.—SMITH (*Boston Med. and Surg. J.*, 1925, 193, 387) summarizes very well indeed the present-day conception of a cardiologist as to the treatment of syphilis of the heart and aorta. His summary is conservative and agrees well with the opinion held by the majority of the men who are primarily interested

in cardiac conditions, although it differs considerably from the opinion of those who are interested primarily in the treatment of syphilis. The summary of the author's conception of the treatment of heart disease due to syphilis is as follows: Arsphenamin is valuable and should not be deleted from the treatment of cardiovascular syphilis, but mercury and iodids are the indispensable drugs in the treatment of these cases. Treatment should be begun with mercury and potassium iodid and should be continued some weeks, and then only after careful consideration of the clinical picture should arsphenamin be given. The initial dose should be very small and should be gradually increased to not more than 0.3 gm. If tolerated, repeated courses should be given, as in the treatment of syphilis generally. Arsenic is a dangerous drug with which to begin treatment. The danger increases in relation to the size of the dose and the organic changes present in the aorta and heart. No definite routine can be laid down or followed. In cases with marked renal insufficiency arsphenamin may be a safer drug than mercury. The author says that in the treatment of syphilis we should not forget that the patient has a damaged heart. General management of the case may be as important in determining the duration of life as the treatment of syphilis itself. Occasionally a case may be seen in such a desperate condition that one is justified in instituting the most intensive treatment in hopes of saving the patient's life. The author concludes with the statement that when the patient shows no systematic improvement with mercury and iodids he is extremely skeptical as to any benefit from arsphenamin.

Comparison of the Kahn with the Wassermann Test.—In the past few years a considerable amount of literature has accumulated concerning the value of the Kahn precipitation test for syphilis. The greater part of this work has confirmed Kahn's studies of his test and has shown that this test and the Wassermann test match each other very closely. FAUPEL (*Bull. Johns Hopkins Hosp.*, 1925, 37, 170) has tabulated the findings of nine observers, which shows that they are for the most part very close indeed, averaging roundly about 90 per cent agreement. In her series of 400 examinations of the blood of syphilitics, she finds that 90 per cent showed absolute agreement; 3.8 per cent, relative agreement; 5 per cent, partial agreement; only 1 per cent showed absolute disagreement. The coefficient of correlation of the heart series was found to be 0.79. Although this paper presents nothing new, it does give additional confirmatory evidence as to the value of this simple test for the presence or absence of syphilis. Papers such as this would help to establish the value of this test, and there can be no question but that it is a test of value. Kahn's precipitation test may be performed with a minimum amount of technical laboratory knowledge. A very small amount of equipment is necessary, and there is the additional advantage that the test may be performed in a very few minutes. As the author points out, this test can be well used in general dispensaries, and the results may be given before the patient has left. It may be carried out by practising physicians, as there is no necessity of keeping on hand rabbits nor an expensive incubator is not necessary. Incidentally, the author does not think the test is applicable to spinal fluids.

Carbohydrate Tolerance in Myxedema.—HILL, BRETT and SMITH (*Quart. J. Med.*, 1925, 18, 327) draw the following conclusions from their studies of carbohydrate tolerance in thyroid disease: (1) Severe cases of exophthalmic goiter tend to have high and prolonged blood-sugar curves and to have glycosuria. (2) Myxedematous patients also give a blood-sugar curve which is higher and more prolonged than in normal persons; there is rarely glycosuria, and it is suggested that the renal threshold is raised in this condition. (3) The fasting level of blood sugar is in the majority of myxedema cases within normal limits. (4) No relationship between length of history of symptoms, clinical signs, the basal metabolic rate and the carbohydrate tolerance test could be established. (5) Thyroid extract does not raise the fasting level when myxedematous patients are treated; its general effect is to lower the blood sugar and to quick the curve. (6) The carbohydrate tolerance test is not so efficient a method of controlling the treatment of myxedematous patients as is the determination of the basal metabolic rate.

SURGERY

UNDER THE CHARGE OF

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Appendicitis in the Aged.—MAES (*New Orleans Med. and Surg. Jour.*, 1925, 78, 117) writes that appendicular disease is relatively infrequent in patients over fifty years of age, but is accompanied by a very high mortality. After the thirtieth year the histology of the appendix, as of the tonsil, changes, and to this change may be attributed the early thrombophlebitis and the massive gangrene so frequently found at operation or at autopsy. The objective symptoms give no hint of the gravity of the intraabdominal pathology and the naturally lowered resistance of elderly persons, plus organic diseases of the heart or kidneys, makes the prognosis always a serious one. Ileus, pyemia and septicemia are frequent complications. Early diagnosis and prompt treatment, in which free drainage is of prime importance, furnish the only possible means of reducing the mortality. Since the patients who develop fecal fistulæ usually recover, and since a late enterostomy usually does little good, it is suggested that a Pezzer catheter or a Paul tube be left in the cecum at the time of operation.

Postoperative Parotitis.—SIMONS and RAND (*New Orleans Med. and Surg. Jour.*, 1925, 78, 129) say that every postoperative parotitis is a potentially lethal condition until it proves to be benign. This acute

inflammatory state occurs three to five days after operation and subsides in the same length of time. In acute circumscribed suppurative parotitis with local and systemic reactions intensified, pus can be pressed out of Stensen's duct in the absence of obstruction. Acute profuse suppurative parotitis is rare. Suppuration occurs in from thirty-six to forty-eight hours, with marked swelling of the face and severe general symptoms. Mortality is about 30 per cent. Gangrenous parotitis is very rare and almost always fatal. To await the spontaneous evolution of parotitis is to jeopardize life. When the condition is surgical early operation with free incision and open drainage is indicated. The greater the involvement of the face and neck structures, especially in gangrenous parotitis, the greater the need for thorough exposure.

Clinical and Surgical Aspects of Renal Neoplasms.—HYMAN (*Surg., Gynec. and Obst.*, 1925, 41, 299) states that hypernephroma is the predominating type of kidney tumor. More than 50 per cent of his cases occurred during the fourth and fifth decades. The classical or primary symptoms of kidney neoplasms are pain, hematuria and tumor. Later on cachexia develops, metastases appear and evidences of venous stasis, the result of tumor compression, manifest themselves. Kidney tumors are extremely malignant. The author emphasizes the difficulty of early diagnosis, the disproportion between early symptomatology and pathologic findings and the importance of pyelographic data. While early diagnosis, based on classical symptoms does not necessarily indicate a favorable prognosis, extension into the vein does not render the prognosis hopeless. The ultimate mortality ranges between 65 and 75 per cent, and the only way to effect a reduction of this high rate at present would be to use the cystoscope and to make pyelograms, not alone in every case of hematuria, but in every case complaining of intractable sciatica and lumbago.

A Symposium on the Diagnosis and Treatment of Backache.—RUGH (*Therap. Gaz.*, 1925, 49, 609) states that a study of roentgen-ray photographs, which included the lumbar, lumbosacral and sacroiliac regions, showed that there is some anatomical abnormality or variation in bony conformation present in about 85 per cent of apparently normal individuals. This includes irregularity in size, shape and relations of the processes, articulations and bodies of the vertebræ, the sacrum and the ilium. A firm strapping about the pelvis, keeping the straps between the iliac crest and the femoral trochanter is a very reliable diagnostic factor in all sacroiliac conditions, as it provides prompt relief, and a permanent cure may then be secured by a properly applied belt or corset. Tuberculosis of these bones is not uncommon and gives a history of a gradually progressive process with increasing disability and pain and the onset of deformity with frequently an accompanying abscess. The roentgen ray is diagnostic later in the process, but not early. Neoplasms in this region may be primary or secondary. The history and careful roentgen-ray studies are necessary to a diagnosis and the prognosis is bad. Surgery is useless. Pain in the middle of the back, over the sacrum and lumbosacral region, should always direct attention to the prostate gland and seminal vesicles.

Deep Roentgen-ray Therapy of Mammary Carcinoma.—EVANS and LEUCUTIA (*Am. Jour. Roentgenol.*, 1925, 14, 135) say that the final outcome of mammary carcinoma depends on the manner of dissemination of the disease. Cancer spreads by embolic invasion of the lymph vessels and lymph glands, by extension, by continuity in the way of slow permeation of the lymph plexuses around the primary lesion and by embolic invasion of the blood stream. All operable carcinomas should be operated upon. The surgical procedure should be followed within ten to twelve days by postoperative roentgenotherapy. The site of the primary lesion, the adjacent glands and the microscopically permeated cancer area should be covered by radiation. All inoperable carcinomas should be treated by radiation. In instances apparent cures, and in all cases palliation and prolongation of life, are obtained. Cancer immunity exists. Radiation therapy may increase this defense mechanism of the organism.

Wound Healing in Syphilis.—MENNINGER (*Am. Jour. Syph.*, 1925, 3, 445) claims that 22 surgical cases in which syphilis is present, as indicated by strongly positive Wassermann tests are here presented. In 4 cases receiving preoperative treatment, 3 presented some postoperative difficulty. All had positive Wassermann tests at the time of operation; despite the fact that they may have been treated, they cannot be operated upon with absolute impunity, although their postoperative courses may be uneventful. Untreated cases of active syphilis may develop postoperative difficulty in wound healing. The role played by syphilis is not determined. In some cases pyogenic bacteria of low virulence grow luxuriantly. In others there is a poor tendency to union without gross infection and in others there is no postoperative difficulty whatever.

The Use of Iodin in Goiter.—LAHEY (*Boston Med. and Surg. Jour.*, 1925, 11, 487) writes that the use of iodine in the treatment of goiter has always been common. Iodine is useful, however in 2 pathologic thyroid states, 1 in regions where goiter is endemic and the iodine content of the drinking water is low, and as a measure to prepare toxic thyroid patients for operation. Its use as a prophylactic measure in the form of sodium iodide, 1 gr. per day for one week out of every six months, has been convincingly demonstrated by Kimball and Marine in their experiments with the school children of Akron, Ohio. The introduction of Lugol's solution by Dr. Henry S. Plummer as a method of preparation for operation in exophthalmic goiter marks a step of forward progress in the surgical management of this disease. It has practically eliminated preliminary pole ligation, and has made it possible to complete the operation of subtotal thyroidectomy in one stage upon a great majority of our patients.

The Value of Blood-pressure Determinations in Major Surgery.—ADAMS (*Texas Jour. Med.*, 1925, 21, 241) states that surgery from the start tends to lower the blood pressure, and this depression in the average handicapped patient coming for operation begins from five to twenty minutes prior to any other symptom indicative of the approaching shocked state. The use of several large packs and loss of blood

will cause a temporary drop in the systolic and diastolic pressures. All three general anesthetics now in use—ether, nitrous oxid—oxygen and ethylene oxygen—cause a rise of blood pressure during the first fifteen minutes. But deep ether anesthesia continued for over one hour in any patient except the young adult of good cardiac compensation nearly always causes a distinct drop in both systolic and diastolic pressures and a well-recognized increase in pulse rate. It is true that ether is a so-called cardiac stimulant, but this is not the case when the amount is used that is necessary to produce complete and absolute relaxation. Nitrous oxid and ethylene seem to produce more gradual changes in pulse, respiration, systolic and diastolic pressures. Spinal anesthesia nearly always produces such an extreme drop in blood pressure that it is contraindicated in low-pressure cases. Novocain produces distinct drop in pressure when used in large amounts as a local anesthetic.

THERAPEUTICS

UNDER THE CHARGE OF
SAMUEL W. LAMBERT, M.D.,
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The Action of the Intravenous Injection of a 40 Per Cent Solution of Urotropin.—Since Vogt (*Ztschr. f. Gynäk.*, 1921, vol. 49) first advocated the intravenous injection of a 40 per cent solution of urotropin for the treatment of urinary retention this treatment appears to be the method of choice. RITSCHER (*Deutsch. med. Wchnschr.*, 1925, 19, 776) used this method in the treatment of 69 cases of urinary retention with success in 94 per cent of the cases treated. This method was used to give relief to patients with postoperative retention and also to relieve retention, several days after operation, which was of nervous origin. The usual procedure was to inject 5 cc. of the solution of urotropin on the evening after operation if necessary, and if no result followed to repeat the dose in one-half to two hours. If catheterization was necessary then the danger of infecting the bladder and urinary tract was minimized. Sterile solution of urotropin for intravenous injection are prepared by the firm of E. Schering, and sold in ampules containing 5 cc. This solution must be injected intravenously as intramuscular or subcutaneous injection is followed by painful infiltration.

Indications for the Intravenous Injection of Quinin Salts in Malaria.—Believing that the large variety of methods for the administration of quinin salts in the treatment of malaria indicates that the treatment of this disease is not grounded on a sufficient clinical or experimental basis, WIRSSALADSE (*Ztschr. f. klin. Med.*, 1925, 3-4, 320) directs the attention of the practitioner to the intravenous injection of quinin solutions which was first advocated by Baccelli (*Priforma Medica*, 1890) for the treatment of pernicious malaria. In the treatment of malaria with this method Baccelli warned against generalization, and the author during the years 1920, 1921 and 1922 treated 164 of 952 patients who had malaria by this method, giving 821 intravenous injections,

and in three and a half years treated a total number of 216 malaria patients with 1141 intravenous injections of quinin. He uses a sterile solution of quinin dihydrochlorid, giving 0.5 to 1 gm., dissolved in 40 to 50 cc. of physiologic saline solution. This amount he injects very slowly into the median vein with aseptic technic. Under no circumstances does he use a stronger solution than 0.5 to 1 gm. dissolved in 40 to 50 cc. of physiologic salt solution. But this amount he may give two or three times or five to ten times, rarely as often as twenty times, to the same patient. Stronger solutions or larger amounts are dangerous, but using this small amount of a weak solution the author has seen neither local nor general disagreeable symptoms or complications after 1141 injections. Intravenous injection in all cases has given the best results in a clinical and parasitologic sense, and when all other methods of administration of quinin salts have been ineffective this method is most effective. However, it is by no means indicated in every case of malaria, and according to the author is only indicated in: (1) All pernicious forms of estivoautumnal malaria. (2) Tropical forms of malaria with many parasites in the blood although severe clinical symptoms are absent; such cases may develop severe symptoms at any time, and one or two intravenous injections are given and then other methods of giving quinin are instituted. (3) Acute forms of estivoautumnal malaria with severe symptoms but few parasites in the peripheral circulation; in such cases when one or two injections do not relieve the weakness of the patient he continues to give 1 gm. of quinin dihydrochlorid intravenously daily and 400 to 500 cc. of physiologic saline solution subcutaneously, or 0.5 gm. quinin dihydrochlorid intravenously and 0.5 gm. in 400 to 500 cc. of physiologic saline solution subcutaneously. (4) Quinin-fast forms of acute tertian, quartan or estivoautumnal malaria. (5) All patients who clinically or parasitologically have been found to be reinfected, as these cases often have a severe and protracted course. (6) Chronic and persistent recurrent cases of estivoautumnal, tertian or quartan. (7) Cases of malaria with chronic splenomegaly. The intravenous administration of quinin should be done only in the hospital, and as soon as a tangible result has been accomplished other methods of administration should be started. The author's working rules are: (1) Strict aseptic technic. (2) Cases must fit his classification. (3) Slow injection of the quinin solution. (4) Use of quinin dihydrochlorid in 1 to 2 per cent solution of physiologic saline, that is, 0.5 to 1 gm.; quinin in 50 cc. of saline. Contraindications to its use are arteriosclerosis, kidney disease, obesity, diabetes, lues and any other condition in which the intravenous injection of quinin might be harmful.

The Therapeutic Value of Coramin.—For the treatment of severe cases of collapse with low blood pressure and depressed respiration GUTH (*Therap. Gaz.*, 1925, 9, 626) believes that coramin is superior to camphor. Coramin is a diethylamid of pyridin-beta-carbonic acid and is available in the form of solution for oral administration and in ampules of 1.1 cc. for injection. The highest effect was obtained in ten minutes after intravenous injection, and in thirty minutes when injected intramuscularly. The best results were obtained when both intravenous and intramuscular injections were given. No local or general toxic manifestations were noted from the use of coramin.

PEDIATRICS

UNDER THE CHARGE OF

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Diagnosis of Tuberculosis in Childhood.—SMITH (*Atlantic Med. J.*, 1925, 28, 725), in his experience, found that tuberculosis in the bronchial nodes is the most frequent lesion encountered, and is at the same time very easily overlooked. When a child is seen who is pale and droopy, distinctly undernourished, or with a history of loss of weight, with bright eyes, long lashes and hairy arms and nape, tuberculosis should be suspected. A positive tuberculin test will show that the child harbors the bacillus. Then a temperature record should be kept, so that it might be ascertained if there is activity of the process. A careful physical examination, with special attention to the interscapular region, will often show a tracheal whisper to the fifth or sixth dorsal spine, and occasionally an asymmetrical upper line of pulmonary resonance. The lungs should also be examined with great care, especially in the nipple region and the axillæ, for persistent rales in these locations are suggestive as are signs of dry pleurisy or effusion. The superficial nodes must all be palpated, and the abdomen carefully searched for masses or ascites. The spines and bones must be thoroughly examined. Signs of early meningitis, such as crossness, headache and vomiting, must not be forgotten.

Pyloric Stenosis of Infants.—DAVISON (*Johns Hopkins Hosp. Bull.* 1925, 37, 75) studied 60 cases, 32 of whom were treated medically and 28 surgically: He found that the frequency was highest among white, male, first-born infants of normal birth weight. The case fatality rate was highest among those who were not constipated, in whom the onset was sudden, who weighed less than 7 pounds at birth and on admission, and who had lost the most weight since birth. No fatalities occurred among infants who were overweight at birth or who had gained in weight between birth and admission to the hospital. The fact that the case fatality rate in the medical group was slightly under the rate in the surgical is no reason that all infants with pyloric stenosis should be treated medically, but it is a very good argument against operating on all of these patients as soon as the diagnosis is made, as has been recommended by some surgeons. By selective therapy, rather than by exclusively surgical or medical treatment, the total case fatality rate can be lowered.

Scarlet Fever: Etiology, Prevention by Immunization and Antitoxic Treatment.—PARK (*J. Am. Med. Assn.*, 1925, 85, 1180) states that the antiscarlatinal serum produced by Moser and Savchenko produced the same therapeutic results as that now produced by the Dochez method or by the subcutaneous injection of known dose of toxin. The value of the earlier products was greatly handicapped by the lack of any

means, such as the Schultz-Charlton or the Dick methods, for estimating their antitoxic potency. Because of this lack of knowledge serum weak in antitoxin was undoubtedly given with disappointing results. The antitoxic serum should be given in sufficient amounts as early in the disease as possible. When thus given the result in most cases is strikingly favorable. The early use of antitoxin probably frequently prevents the development of complications. Antitoxin is useless after the rash has disappeared, and has no effect on later septic complications. In moderate cases it should be given intramuscularly. In severe or toxic cases it should be given intravenously. As a rule, a single dose of sufficient size is enough, but in severe cases in which the symptoms return a second dose in from twelve to twenty-four hours is often desirable. It is too early to state whether the serum should be given in very mild cases, since the serum sickness is often more annoying than the scarlet fever. The refined antitoxic serum produces fewer and less severe rashes than the unrefined, and should in time be the only preparation employed. A unit should be adopted, so that the results from different dosages may be compared. The one suggested at a recent meeting of immunologists in Washington seems to be suitable. One unit is defined as the amount of antitoxin that neutralizes 100 skin-test doses of Dick as determined by an intracutaneous test in man. A dosage between 2000 and 10,000 units will probably be sufficient in the great majority of cases. A few of the failures of antitoxin may be due to streptococci that produce other toxins than are neutralized by the antitoxin used. This is an interesting problem for future study. Whether it will be of marked advantage to combine an antimicrobial serum with the antitoxic serum is still doubtful. A serum of this class used in the past has given only doubtful results, but combined with antitoxin it may add to the benefit produced.

The Phenomena Concerned with Reactions following the Transfusion of Blood.—KORDENAT and SMITHIES (*J. Am. Med. Assn.*, 1925, 85, 1193) observed that if whole blood is employed in transfusion, and if the donor blood is carefully selected posttransfusion reactions are relatively rare, and was less than 4 per cent in the series of the observers. Posttransfusion effects of a harmful type may be minimized if donors are selected not only with respect to their place in the arbitrary four groups of Moss's classification, but also when donor and recipient bloods are cross-grouped for estimation of their agglutinin-agglutinogen content. There are three types of posttransfusion effect: (1) The immediate, or hemolytic; (2) the delayed, apparently not hemolytic, but proteolytic; (3) the constitutional, or nonhemolytic. The subjective and objective phenomena of hemolysis can be explained by the effects of lysed blood on the peripheral capillary bed. The mechanism of these capillary responses is similar in kind, but greater in intensity, to peripheral vascular phenomena observed in Raynaud's disease, purpura and the like. The nonfulminant and delayed posttransfusion reactions are caused by anaphylactoid protein phenomena, but not necessarily of specific nature.

Energy Metabolism of Premature and Undersized Infants.—MARSH and MURLIN (*Am. J. Dis. Child.*, 1925, 30, 310) determined the energy

metabolism in 82 observational periods on 21 premature and under-sized infants, including 5 pairs of twins. The average basal respiratory quotient was low, 0.74, through the fifth day, rose to 0.79 on the sixth day, but never above this figure through the ninth day; whereas the quotient for a child in good nutritive condition, at least after the first week, should be about 0.85. The basal metabolism of these 21 infants averages 6.48 calories per hour, or 26.25 calories per square meter and 2.04 calories per kilogram per hour. On the basis of body surface, this is lower than the basal figure for full-term normal infants by 2.91 calories per hour. On the basis of the weight, it is slightly higher than for full-term infants, but is lower than would be expected if the metabolism per unit of surface were as high as it is for full-term babies. When the basal metabolism per square meter is averaged according to days of age there is a fluctuation during the first week, the lowest value coming on the seventh day with a higher value on the eighth and ninth days. Each day the metabolism is definitely lower than for the value obtained for normal babies born at term. Increases in heat production with activity varied from 2.5 per cent, with slight restlessness, to 40.3 per cent, when the child cried 39 per cent of the time. In a limited number of periods, and all on infants one month or less premature, the observation made previously for full-term babies, that is, crying 1 per cent of the time increase the metabolism 1 per cent, seems to hold fairly good. It seems impossible to obtain a basal period without food with which to compare a subsequent period with food for dynamic action. A few cases with variations in the amount of food fed to the same infant on the same day or on different days show a definite increase in heat production with more food, and when all the cases with small feedings are averaged and compared with the average of the cases following large feedings we find that an increase of 42.1 gm. of food increased the metabolism 5.19 calories per square meter per hour, or 21.3 per cent. The increased feedings on the basis of weight being nearly three times the increased feedings from which the dynamic action in full-term newborn infants were studied, it is not surprising to find the dynamic action nearly three times that noted in the previous study of these authors.

GYNECOLOGY

UNDER THE CHARGE OF

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Coincidence of Uterine Tumors.—The frequent coincidence of different tumors in the same uterus induced FRANKL (*Am. J. Obst. and Gynec.*, 1925, 9, 745) to investigate the material of the First Gynecologic Clinic

of Vienna over a period of fifteen years. Among 1878 cases of myomata he found 46 sarcomata. He believes the relationship of these tumors may be: (a) The same uterus may contain a myoma and a sarcoma entirely independent of each other; (b) a myoma may be destroyed by a sarcoma which develops outside of it; (c) most frequently, the sarcoma develops within the myoma, growing from the center to the periphery, so that the myoma becomes destroyed and is replaced by the sarcoma. During the time that this series of 1878 cases of myoma were observed, in the same clinic there were 1036 cases of carcinoma, 919 of the cervix and 117 of the body. In 72 cases myoma and carcinoma were found in the same uterus. Among 919 cases of cervical cancer 62 uteri also contained myomata. Among 117 cases of body cancer 10 uteri also contained myomata. Basing the findings on myomata, we see that in 3.8 per cent of all myomata, carcinoma occurs at the same time. The number of body cancers, as related to the entire myoma material is 0.5 per cent. The number of cases of cervix cancer in relation to the entire myoma material is 3.3 per cent. Starting with carcinoma, the author found that in 6.8 per cent of the uterine cancers operated upon myoma was also present. These figures afford an entirely different picture from those given by other authors, whose data are based upon insufficient material, or are based on myoma examinations and therefore are not reliable. Their findings made it necessary to construct special theories to explain the pretended frequent occurrence of carcinoma of the uterine body, cases of myomata and the frequent occurrence of carcinoma in the myomatous uterus in general. But if we find that 6.8 per cent of all operated uterine cancers show myomata at the same time it is certainly no more frequent than myomata in the noncarcinomatous uterus. On the other hand, the frequency of 3.8 per cent of all myomatous uteri being carcinomatous at the same time is relatively high compared with the general frequency of cancer of the uterus. The author concludes that carcinoma of the body of the uterus is no more frequent in the myomatous uterus than is carcinoma of the cervix. In regard to the simultaneous occurrence of carcinoma and sarcoma in the same uterus, the author has seen 8 such cases, in most of which he believes that the tumors first existed side by side and later one grew through the other.

Pelvic Inflammatory Disease.—A statistical study of 294 cases of adnexal inflammation which were operated upon in the Gynecologic Division of the Breslau General Hospital during the past ten years has just been presented by MANNHEIM (*Zentralbl. f. Gynäk.*, 1925, 49, 1471). In this series two-thirds of the cases were treated by means of a radical operation and one-third received a conservative operation. Forty-five per cent of the patients were married, widowed or divorced; 7 per cent were prostitutes; 48 per cent were single. Classified according to age, 56.4 per cent were under thirty years, 24.8 per cent were between thirty and thirty-nine years, while 18.8 per cent were forty years or older. Considering the etiology, 43 per cent were gonorrheal, 7 per cent were suspicious of gonorrhea, 5.8 per cent were septic or sapremic infection, 1.4 per cent were tuberculous, while in 43 per cent the etiology was unknown. In the series 228 patients were subjected to laparotomy, while 66 were operated upon *via* the vagina, but

it is significant to note that the percentage of vaginal operations has markedly decreased in the last few years. This is in keeping with the views of most gynecologists, since the abdominal operation is much more preferable than the vaginal except in the occasional rare case. Under the heading "conservative operation" are included such methods as simple incision of the tubes, release of adhesions, removal of one adnexa either alone or in combination with salpingostomy on the opposite tube, removal of both adnexa, conserving the uterus and one ovary, and finally conserving only one ovary. In spite of all these various conservative methods, an analysis of this series by years shows that the tendency in this clinic is to do more radical operations and fewer conservative ones every year. This is justified by the results obtained, since in the radical group there were 90 per cent cures, 0.5 per cent reoperated upon and 3 per cent mortality, while in the conservative group there were only 65 per cent cures, but 9 per cent reoperated upon and 3 per cent mortality. As a result of his study of the subject, the author concludes that the radical operation is to be preferred in most cases, as it will give a greater number of satisfactory end results, fewer cases which will require secondary operation and practically the same mortality as the conservative method, while the percentage of complications is the same in both methods.

Epithelioma of the Vulva.—It is a noteworthy fact, states SCHREINER (*Arch. Clin. Cancer Research*, 1925, 1, 45), that the majority of gynecologists are extremely pessimistic as to the end results in the treatment of epithelioma of the vulva and clitoris. All forms of treatment in the past, whether by surgery, irradiation or coagulation, have yielded primary results that were gratifying, but leave much to be desired in the mitigation of suffering caused by recurrences in this class of patients. In a study of 31 cases of vulvar carcinoma at the State Institute for the Study of Malignant Disease, Buffalo, N. Y., it was found that the treatment with surface applications of radium and low-voltage Roentgen rays is inadequate and has been abandoned. The implantation of radium seeds in these lesions supplemented with high-voltage Roentgen rays has proven extremely painful to the patient, causing a great deal of suffering, especially from six to eight weeks after the treatment. The combination of implantation of the primary lesion with seeds and at times seed implantation in the metastases, with high-voltage Roentgen rays in addition, followed by electrocoagulation (endothermy) is the method of choice both for the comfort of the patient as well as the end results.

Cancer of the Vagina.—In a series of 33 cases of cancer of the vagina studied by SCHREINER (*Arch. Clin. Cancer Research*, 1925, 1, 41) there were 29 epitheliomas and 4 adenocarcinomas. For purposes of study and treatment the cases were divided into two groups: Early cases, in which the tumor is confined to the mucous membrane of the vagina, more or less localized, and far-advanced cases, which involve a large portion of the vaginal wall and have infiltrated the rectal or bladder walls, or metastasized in the groin or broad ligaments. The surgical treatment of cancer of the vagina offers practically nothing on account of the anatomic difficulties, so any form of treatment that offers a

possible relief, whether only symptomatic or only palliative for a time, is of value. The results in this series were extremely poor because the majority of the cases were so far advanced. The effort was made to administer as much radiation against the lesion as possible, keeping in mind the dangers of fistula formation. The dosage of radium in these cases varied from 150 mc. hrs. to 2500 mc. hrs., filtered through 2 mm. brass and 1 mm. rubber supplemented with high-voltage Roentgen rays and radium packs applied over the symphysis or perineum sufficient to bring the total dose up to 120 to 135 per cent, 3 cm. from the tubes. In this series 4 out of 8 cases in Group I have been clinically well for periods varying from two months to two years and eight months. Two of 21 far-advanced cases have been well, 1 for three years and the other for one year and seven months. In the 4 cases of adenocarcinoma of the vagina 3 died from the disease and 1 has improved. The author believes that the application of radium against the lesion in the vagina, supplemented with high voltage Roentgen ray, offers more than any other known treatment for cancer of the vagina.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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Cerebrospinal Fluid as Index of Otorhinogenic Intracranial Complications.—Describing the normal spinal fluid as a clear, colorless, sterile fluid, containing sugar but no globulin, and in the adult not more than 8 lymphocytes per c.mm., YERGER (*Jour. Am. Med. Assn.*, 1925, 85, 424) reported the results of a study on 155 cases of meningitis, 43 cases of lateral sinus thrombosis, 35 cases of brain abscess, 8 cases of labyrinthitis, 4 cases of extradural abscess, 2 cases of cavernous sinus thrombosis and 1 case of subdural abscess. It was learned that although the cerebrospinal fluid is a reliable index of some of the intracranial complications of otorhinogenic origin, even being pathognomonic in some instances, it may be misleading, and should not be relied on to the exclusion of other dependable clinical signs indicative of intracranial involvement. The knowledge obtained from examination of the cerebrospinal fluid may be of value either in a positive or a negative manner. A negative finding at once differentiates a meningismus from meningitis, and it usually eliminates meningitis, brain abscess, subdural and extradural abscess. However, one negative finding in a case of threatened or manifest intracranial complication should not be considered final. A sterile cerebrospinal fluid with a low cell count (from 25 to 250) excludes a suppurative meningitis, but throws suspicion on the presence of an extradural or brain abscess; in a medium cell count (from 250 to 2500) one should suspect a subdural or brain abscess or meningitis; but in the high (over 5000) and very

high (over 10,000) cell count a diffuse suppurative meningitis is usually present. A diffuse meningitis is considered clinically proved when bacteria are found in the cerebrospinal fluid. In a circumscribed meningitis, serous or suppurative, of otorhinogenic origin the cerebrospinal fluid returns to normal after the removal of the focus of infection, as extradural or brain abscess; but when drainage is insufficient it does not return to normal, and when complicated by an acute diffuse purulent meningitis there occurs a sudden and marked increase in the polymorphonuclear leukocytes, with or without the association of bacteria. Diffuse septic (bacterial) suppurative meningitis is associated with a high polymorphonuclear cell count plus the invading bacteria; it is frequently the sole otitic intracranial complication, but it may be associated with brain abscess or septic sinus thrombosis as a terminal complication.

Treatment of Fibromas of the Nasopharynx: Report of Thirty-two Cases.—NEW and FIGI (*Ann. Otol., Rhinol and Laryngol.*, 1925, 34, 191) reported the effects of treatment on hard fibromas which occurred in the nasopharynges of 32 patients. The ages varied from ten to thirty-one years, the average being eighteen and a half years. Twenty-nine (90.6 per cent) were less than twenty-five years of age at the time of examination, and 3 (9.3 per cent) were between twenty-seven and thirty-one years. The activity of the tumor seemed to be directly related to the age of the patient, although the fact that operations had been performed in many instances made it hard to determine this point. Twenty-eight of the tumors occurred in males and 4 in females. The average age of the males was nineteen years and that of the females fifteen years. The duration of symptoms previous to examination was from two months to six years. Five patients had had symptoms for less than one year, 9 for more than two years. Twenty-three of the 32 patients had been operated on from one to twelve times prior to their examination at the Mayo Clinic. While the authors recognize that the "Type of treatment to be selected for new growths is that which will give the best end results in each particular case," and classify the therapeutic procedures into three groups: (1) Surgical, (2) cautery or diathermy and (3) radium and roentgen ray; they feel that in nasopharyngeal fibromata radium is the treatment of choice. Before radium was used (1910 to 1915) 8 patients in the series were observed, 5 of whom were operated upon by the avulsion method. Of these 2 died and no trace of the other 3 could be found. From 1915 to 1924 24 patients with fibroma of the nasopharynx were examined. Twenty-three were treated with radium, which was applied by any of three methods, with a T-shaped lead applicator, by inserting steel points containing radium emanation or the element directly into the tumor or by implanting emanation seeds in the neoplastic tissue. The dosage depended largely upon the size of the tumor. It was found that by the use of radium the usual operative mortality was eliminated. In most of the cases the tumor cleared up entirely, and in others it was held in check during its period of activity. That the treatment, and not the natural regression of the tumor, was the important factor in the cure, the authors mention that 11 (73.3 per cent) of patients were less than twenty-three years of age when cured, and 4 (26.6 per cent) more than twenty-three years of age when cured.

RADIOLOGY

UNDER THE CHARGE OF

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Chronic Infection of the Gastrointestinal Tract: Its Roentgen-ray Manifestations.—There is a tendency of roentgenologists, according to EASTMOND (*Am. J. Roentgenol. and Radium Therap.*, 1925, 13, 541), to disregard the manifestations of gastrointestinal disorders when they involve anything but the detection of ulcer, cancer and diseases of the gallbladder or appendix. There are important manifestations of chronic infection that should be recognized. There are abnormal appearances seen on the lesser curvature of the stomach that are neither ulcer nor malignancy, but occur in the form of more or less localized filling defects. These show the presence of congestion, round-cell infiltration and fibrosis, and although it is not an erosive condition the author prefers to call it ulcerative gastritis. There is also the condition called "stiffening," characterized by having no localized serrations or defects in the marginal filling of the stomach, but the pyloric extremity for a distance of 2 or 3 inches is smooth, contracted and shows alteration in the character of the peristaltic waves. In the duodenum are seen many deformities, nonulcerative in character, due to the same process seen in the stomach, namely, a chronic round-cell infiltration with fibrosis and diminishing of the elasticity of the bowel. There may be small craters in the mucosa of the first portion of the duodenum, and these should be called ulcerative duodenitis. The adhesions so often considered secondary to pericholecystitis are really due to the duodenitis. In the second portion of the duodenum there is a coexistence of disease which is very common, and here adhesions result from a periduodenitis as well as a cholecystitis. In the ileum, besides the numerous conditions recognized, there is an intrinsic ileitis that has been overlooked, which is also a condition of congestion, with round-cell infiltration, fibrosis and more or less cicatricial narrowing. The cecum shows changes of infiltrative or sclerotic type and may include the ileocecal valve, causing incompetency of the valve. The colon also shows chronic sclerotic changes, and it is recognized by the lack of elasticity or irregular contraction, most commonly seen in the sigmoid.

An Analysis of Bone and Joint Lesions of Known Syphilitic Origin.—In view of the great confusion existing in regard to bone lesions, especially of syphilitic origin, CAMPBELL (*Radiology*, 1925, 5, 122) has analyzed a number of known syphilitic bones and joints. Syphilis of bones and joints is usually found only in the tertiary stage. The records show that trauma may induce typical luetic lesions in syphilitic subjects. The syphilitic process is first proliferative (periostitis), a precursor to the later or degenerative (osteomyelitic) stage. Some

cases were found to have more than one focus. In the roentgenography of bone syphilis, bear in mind that the distribution may be local or diffuse in any part of the bone, or there may be multiple foci in two or more bones; that the first change is a fuzzy proliferation of periosteum, sometimes stratified; that the bone blister may occur and also form a bone ulcer; that there may be a fine bone formation called "lace work;" that the bone cortex may enlarge and encroach upon or obliterate the medulla. The degenerative or osteomyelitic stage gives massive enlargement of the bone, with areas of increased opacity alternating with areas of destruction, without atrophy. The opacity so characteristic of syphilis is an attempt at hypertrophy. Hypertrophy of the cortex is very common in syphilis and should always be looked for when syphilis is suspected. In syphilitic arthritis there may be changes in the soft structures before the bone shows any lesion. Bone syphilis usually shows gross changes before the subjective symptoms appear, while in joint syphilis the symptoms of pain, muscular spasm and disability are far less than the physical and roentgenologic signs would indicate. Taking this fact and the blood Wassermann into consideration, the author believes the following changes to be most suggestive: An increase in density of one of the bones of the articulations; extra-articular proliferation of the periosteum of one of the bones forming the articulation; punched-out area on lateral or medial aspects; fuzziness of joint surface; large opaque area within the cancellous bone near the articular surface and extensive bone destruction without atrophy. Joint syphilis tends to spontaneous recovery without ankylosis. In congenital syphilis the joint lesion was found more to be common than the bone lesion. The author reported 33 cases of joint lesions with a positive Wassermann, but without any clinical or roentgenologic symptoms of syphilis, which were unresponsive to antisiphilitic treatment. Therefore, the fact that a Wassermann is positive does not prove that all bone and joint lesions present are syphilitic.

Myeloid Myelomata.—MOORE (*Radiology*, 1925, 5, 18) reports 4 cases of myelogenic tumors classified as: (1) Chloroma of myeloid type, and considered a myelocytoma; (2) plasma-cell type, or plasmocytoma; (3) 2 cases like the second group, but differing in many ways. The plasmocytoma was the ordinary and usual form of multiple medullary myeloma, and had as its characteristics the production of ovoid or rounded rarefied areas in bones, giving the appearance of being expanded from within. In the second case, that of multiple myeloma of plasma-cell type, the process seemed to be confined mostly to the long bones, and showed no sign of bone production or expansion. The changes in the bone consisted of small circular rarefied areas of sharp outline and little tendency to become confluent, suggesting the existence of multiple discrete small tumors. The blood count and smear was not unusual, except that there were from 3 to 7 per cent myelocytes present. The histologic report of the bone marrow showed a strong suggestion of erythroblastic origin for the tumor, but it was finally considered a plasma-cell type of myeloma. The third case showed successive development of tumors of the clavicle, forehead and right sacroiliac region. These were treated by deep Roentgen-ray

therapy, to which they responded very readily. Roentgen-ray examination at this time revealed pathology in many bones, characterized by a rarefaction and destruction of bone, but the outline of the rarefied areas was not clear cut; and, where multiple, these tumors tended to fuse. Later a tumor mass was removed from the abdominal wall which was found to be a myeloid myeloma of plasma-cell type. After reëntry to the hospital several times, receiving relief from symptoms by deep Roentgen ray, the patient finally became much worse and died. The fourth case was that of a man coming to the hospital with a pathologic fracture of the humerus and a white blood cell count of 85,100, of which 22 per cent were myelocytes, mostly basophilic. There was a large mass in the humerus, but no other bone lesions. The arm was amputated and the pathologic report was myeloma. The patient was treated for leukemia with benzol and Roentgen radiation with much benefit. He reëntered the hospital many times with new masses and bone involvement, which for a while responded to treatment, but finally overwhelmed the patient, causing death. The clinical and postmortem diagnosis of this case was leukemia with peculiar manifestations, yet it was undoubtedly a chloroma of the myeloid type presenting malignant tendencies, and therefore is a unique case. The author considers these 4 cases as four separate and distinct malignant conditions of bone marrow that are distinct from leukemias, and are not sarcomatous but of hematogenic origin.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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The Relation of Social Work to Psychiatry.—TRUIT (*Am. J. Psychiat.*, 1925, 5, 103) feels that social workers make more contacts with psychiatric cases in all stages of development than do psychiatrists in private or institutional practice. A greater coöperation is urged between psychiatrist and social workers in order that the former may become familiar with the social aspects while the latter grasps some of the psychiatric aspects. The proper coöperation should bring about a more comprehensive social psychiatry.

Studies of Gastric Secretion and Motility in Mental Patients.—The study is a continuation of work reported in 1923, in which it was tentatively concluded that depressing emotions inhibited gastric and even duodenal secretion; that mental exaltation seemed to favor gastric secretion; that somatic and hypochondriac delusions bore no relation to secretory variation. In all, 191 women were studied, presenting a great variety of reactions from depression to elation; some nonaffected cases were also included. Of the whole series 13 per cent

were overweight, 31 per cent normal and 56 per cent underweight. FARR, LÜEDERS and BOND (*Am. J. Psychiat.*, 1925, 5, 93) conclude, however, that malnutrition was not correlated with any of the effective groups *per se*. The effective groups showed basal metabolism scattered evenly on either side of normal, while the noneffective patients tended to have low basal metabolism. Seventy per cent of the patients with elongated or ptosed stomachs were underweight, while only 30 per cent of those with normally located stomachs were thus classified. They conclude, however, that the position of the stomach is primarily an expression of habitus and related only secondarily to nutrition. Position and atony seem to have less relation to emptying time of stomach than would be expected. Colon emptying was slightly delayed in depressed patients, but in such small degree as to warrant caution in conclusions. Sixty per cent of patients with hyperacidity or hypoacidity were underweight. Forty per cent of patients with achlorhydria were underweight. In 50 per cent of achlorhydria cases pernicious or severe anemias, gallstone disease, carcinoma, nephritis, etc., were present, and in 25 per cent more of this group some of these diseases were possibly present. Only 7 per cent of the hyperchlorhydria or hypochlorhydria cases had evidence of associated organic diseases. More of the depressed cases tend to have low gastric acidity or achlorhydria. A very high acidity was found in some patients after excitement incident to doing the tests. The authors feel that acute emotions (anger, fear, etc.) probably affect gastric secretion more than "habitual feeling tone." A chart is given which gives all the data.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Analysis of the Fecal Flora in Thirty-three Cases of Pernicious Anemia.—MOENCH, KAHN and TORREY (*Jour. Infect. Dis.*, 1925, 37, 161) say that a bacteriologic analysis of seventy-two stool specimens from 33 cases of pernicious anemia of various durations showed in practically every case an unusually large number of viable organisms, of which *Bacillus coli*, streptococci, *Bacillus welchii* and, at times, *Bacillus acidophilus*, were the most prominent types. These findings indicated that the flora of the large intestine is of an actively growing, nonproteolytic, fermentative type. The most significant feature revealed by these examinations would seem to be the uniformly high counts for *Bacillus coli* and *Bacillus welchii*. The numbers of both

these organisms averaged much higher than for normal persons or for other pathologic conditions. Although streptococci were also very numerous, they conformed to the normal intestinal types, no representative of the hemolytic group being encountered. Pure cultures of *Bacillus welchii* strains were isolated from 26 of these cases, and subjected to differential tests. Representatives of the four fermentative types of Simond were encountered, but Type I occurred with the greatest frequency (50 per cent). These several strains differed also in the amount of hemolysin produced. Although most of them were strongly hemolytic, it could not be said that they exhibited in general greater potency in this respect than did strains from normal human intestines. All of the strains tested showed a high degree of pathogenicity, but this is also frequently true for strains from normal sources. It would seem, then, that if these intestinal strains of *Bacillus welchii* are to be brought into etiologic relationship to pernicious anemia it must be on the basis of their excessive numbers and activities, particularly at levels of the intestine where absorption is active and where they are not commonly found only in negligible numbers. In view of Seyderhelm's finding that the flora of the large intestine tends to invade the small intestine in this disease, there is some ground for the latter supposition. Speculation is offered as to the possible significance of active growth of *Bacillus welchii* at the higher levels of the intestine in the production of the pernicious anemia syndrome in view of its well-known capacity to elaborate a potent hemolysin, an irritating acid and neurotoxic substances.

Bacterial Factors in Pyorrhea Alveolaris: IV. *Micrococcus Gazogenes*, a Minute Gram-negative, Nonsporulating Anaërobe Prevalent in Human Saliva.—HALL and HOWITT (*Jour. Infect. Dis.*, 1925, 37, 112) emphasize the frequent occurrence in human saliva of a minute, Gram-negative, nonsporulating, obligate anaërobe. This organism is mainly responsible for the abundant gas generally seen in primary brain medium cultures from unheated saliva. It is identical with the so-called *Staphylococcus parvulus* (Veillon) recently recovered by Holman and Krock, which they thought resembled *Bacillus pneumosintes* in filtrability. The authors, however, disagree both as to its nomenclature and its ability to pass through carefully controlled Mandler filters. *Micrococcus gazogenes* is a minute diplococcus less than 0.5 micron in length and breadth, Gram-negative, nonsporulating, nonmotile and obligately anaërobic. These properties have caused it to be overlooked in most of the modern work on the mouth flora. It is nonpathogenic directly for rabbits, guinea pigs and mice, but it appears to reduce the resistance of rabbits toward other pathogenic microbes. Ten rabbits, immunized by intravenous injection of live cultures, produced powerful agglutinins (all over 1 to 10,000) which distinguished two serologic groups. Group A contained twenty-two strains; Group B, two strains. Holman's cultures fell into Group A. Normal rabbits harbor *Micrococcus gazogenes*, yet produce no agglutinins except under inoculation, but human beings not infrequently produce low-grade agglutinating serums (1 to 40). The strongest serum came from persons free or practically free from gingival lesions, suggesting an immunologic factor relating to this organism in pyorrhea alveolaris.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF OCTOBER 19, 1925

Electrokinetic Behavior of Mammalian Serous Membranes.—STUART MUDD (from the Laboratories of the Rockefeller Institute for Medical Research). Glands may be regarded from one point of view as systems in which a liquid secretion is transported through the capillary interstices between colloidal molecules, micellæ and cells. The capillary interstices are simultaneously traversed by an electric current, the action current of the gland. Does the electric current in such a system influence the movement of liquid? Is the action current too small to have an effect? Is the concentration of salts in the body fluids so high as to abolish electrokinetic effects, which have ordinarily been observed in systems of lower electrolyte concentration? In considering these questions I have had recourse to mammalian serous membranes, which have sufficient similarity from a physical-chemical point of view, but are easier to work with. The membrane is attached over the mouth of the electrode vessel and is bathed inside and out with the perfusing liquid. Current is passed and the rise and fall of the meniscus in the electrode vessel is observed. All liquids tested, whose reaction has been more alkaline than pH 5.9 have streamed through the serosæ toward the cathode. Each membrane has a characteristic hydrogen-ion reversal point, however, on the acid side of which streaming is to the anode, as indicated in communications already published (*J. Gen. Physiol.*, 1925, 7, 389 and 9, 73). The rate of electroendosmotic flow has been found to be proportional to the current strength. The plots of current strengths against volumes of liquid transported in unit time are straight lines *passing through the origin*, indicating that there is no threshold value below which current is ineffective. Any current flow whatever tends to produce liquid flow. The plots of rate of liquid flow against specific resistances of the perfusing buffers do show minimal rates with buffers whose electrolyte concentration is between M/6 and M/10; the actual mean rate of flow when living mesenteries were bathed in whole serum was found to be 0.29 c.mm. per minute per milliampère. The glandular action current then is *not negligible*. Whether it is relatively unimportant or the controlling factor in glandular secretion can only be determined by further experiment.

Estimations of Glomerular Capillary Pressure in the Frog.—J. M. HAYMAN (from the Laboratory of Pharmacology of the University of Pennsylvania). Accurate information concerning the blood pressure in the capillaries in the glomeruli of the kidney is essential for a satisfactory understanding of the processes which take place there. Such information has not hitherto been available. Recent work in this laboratory has shown that the minute structures in the kidney of the living frog may be made accessible both to direct observation and

instrumental manipulation. In the work here reported blood pressures in the glomerular capillaries and afferent arterioles of the frog's kidney have been estimated. Frogs were prepared according to the method of Richards and Schmidt (*Am. J. Physiol.*, 1924, 71, 178) for observation of the renal circulation. A capillary pipette filled with colored salt solution, attached to a Harvard manometer and a device for regulating the pressure, was introduced into Bowman's space. The lumen of the tubule was occluded by pressure. By increasing the pressure within the capsule flow through the capillary tuft could be slowed or stopped. The highest intracapsular pressure at which flow was continuous through at least one capillary throughout the cardiac cycle was taken as equivalent to capillary pressure; that at which a few corpuscles just entered the tuft with each systole, as equivalent to the systolic pressure in the afferent artery. Aortic blood pressure was determined at the same time by another Harvard manometer connected with a cannula in one aorta. Pressures have been measured in the surviving kidneys of frogs during perfusion with oxygenated Hamburger's solution, and also in kidneys of living frogs in which the blood circulation was normal. In general, the pressures in the afferent artery and glomerular capillaries varied directly with aortic pressure. In one perfusion experiment pressure in the aorta was 22 cm. of water; in the afferent arteriole, 18 cm.; in the glomerular capillaries, 10 cm. In another the pressures were 33, 26 and 17 cm. respectively; in a third, 46, 40 and 24 cm. In 94 estimations of glomerular capillary pressure in kidneys with normal circulation the estimations varied at different blood pressures from 4 to 40 cm. of water; the average, 18.6 cm.; 60 of the estimations have been between 11 and 25 cm. of water. In 1 experiment systolic pressure in the aorta was 24 cm. of water; in the afferent arteriole, 19 cm.; in the glomerular capillaries, 15 cm. In another, 34, 28 and 19 cm. respectively, and in another 49, 45 and 30 cm. In the perfusion experiments the pressure in the afferent arteriole averaged 86 per cent of aortic; in the glomerular capillaries, 52 per cent; in living frogs the averages were 86 and 51 per cent respectively. These estimations are appreciably higher than those found by Hill and McQueen (*Brit. J. Exp. Path.*, 1921, 2, 205) by a less direct method.

Allergic Irritability.—PAUL LEWIS and DOROTHY LOOMIS (from the Department of Animal Pathology of the Rockefeller Institute for Medical Research, Princeton, N. J.). In furtherance of our observations on inheritance as an influence in the natural resistance of guinea pigs to tuberculosis infection we have sought to determine the nature of at least some of the qualities involved. Our attention of late has been directed particularly toward those principles which are basic in the modern conception of acquired immunity and which may in some measure be fundamental in natural resistance. The natural approach to these questions, in part, is through a study of the humoral factors in acquired immunity. The antibodies are particularly accessible to observation, are most definitely understood, and hence have served as our starting-point. In view of the consensus of opinion that antibodies actively created in one generation are transmitted to the next only by the female line, and in a purely passive and temporary way, it is plain that any factor involving the activity of these principles must be transmitted in the inheritance as a latent capacity to react to antigenic stimuli

and as a latent capacity only. Experiments intended to measure these latent capacities directly, and in the strict sense of the words, have not yet succeeded. We have, however, been able to study the response to certain stimuli which appear to be directed at the latent capacities, and whose effects are indirectly evidenced by specific antibody production when appropriate antigens are administered. Active infection with the tubercle bacillus at certain stages of its progress in guinea pigs and rabbits is the most effective stimulant we have encountered. Infection with *Bacillus abortus* and with a streptococcus of guinea-pig origin act in the same direction, but less effectively. Likewise treatment with dead tubercle bacilli and with the vital stains trypan blue and trypan red are effective. Under the influence of these stimuli antishoop hemolytic amboceptor and antityphoid agglutinin are produced in the usual manner as evidenced by the curves of formation from day to day. The absolute amounts may be twenty-fold those produced in the absence of such stimuli, and the differences have been maintained over periods sufficing for a series of immunizing treatments. As a result we have been able to secure concentrations of antishoop amboceptor in the guinea pig which have exceeded by ten or more times under stimulation, the maximum amount secured by a comparable series of injections with erythrocytes alone. In this response to these stimuli the inbred families of guinea pigs with which we have dealt appear to differ. In other words, the capacity to react to these indirect stimuli is transmitted in variable degree in the inheritance. Our title requires explanation. In use the phrases "capacity to be immunized," "latent capacity for antibody production," and so forth, have proved cumbersome and not wholly accurate. It has seemed to be better from the academic point of view to recall that it has been customary to say that an animal once subjected to a foreign protein, or once infected or vaccinated with a particular microorganism, is rendered allergic, or put into a state of allergy with reference to that protein or that microorganism. Academically considered, and with relation to physiology, the production of immunity or of hypersensitiveness involves the conception of stimulation, which again is a reflection of a fundamental irritability. We are thus led to the use of the term "allergic irritability" as designating a general characteristic of the animal, on the basis of which it reacts to stimuli of the antigenic class, whether these be helpful, injurious or indifferent to bodily health. Those interested will find a more complete discussion of these questions in the papers of: Wright and Lewis (*Am. Naturalist*, 1921, 55, 20) and Lewis and Loomis (*J. Exp. Med.*, 1924, 40, 503; 1925, 41, 327), and in papers shortly to be published.

Studies of Gastric Juice in Children with Gastrostomies: Colorimetric and Electrometric Determination of the Hydrogen-ion Concentration.—G. KAHN and J. STOKES (from the Department of Pediatrics of the University of Pennsylvania). The object of the present study was to decide the best technic for determining the hydrogen-ion concentration of gastric juice as a preliminary to its application in a study of gastric secretion in infancy and childhood. In a comparison of the electrometric and colorimetric methods, as described by Clark, 100 specimens of gastric contents were examined. In the colorimetric method the dyes, thymol blue, bromphenol blue, methyl red, brom-

cresol purple and phenol red were used. The specimens selected covered thoroughly the range of pH 1.8. Considerable differences were found between the electrometric and colorimetric results on the same specimen. Below pH 3.5 the discrepancy between the two methods was generally less than 0.5 pH, while above 3.5 the differences were much more marked, amounting frequently to 1 pH, or at times even up to 2 pH. For this reason the colorimetric method was considered to be unreliable, unless correction could be made for the above differences. With the hope of eliminating the effects of protein and salts on the dye used, correction of the colorimetric readings was first attempted by diluting the gastric contents. This was unsuccessful. The method of dialysis, as used by Levy, Rowntree and Marriott, and Dale and Evans, was then applied to eliminate the effect of protein on the dyes. Three cubic centimeters of the gastric contents in a collodion sac was dialyzed against 3 cc. of physiologic saline solution for one hour, and the dialysate then tested colorimetrically. Results much more consistent with the electrometric determinations on the unaltered specimens were thus obtained, with a maximum difference between the two of 0.3 pH. It is therefore recommended, where electrometric determination of the CH of gastric juice is not feasible, that colorimetric determination on the dialyzed specimen be carried out. The second part of the problem concerned the evaluation of the stomach tube in the ordinary methods of gastric analysis. The subjects for the study were children with gastric fistulas which had been made because of acid or lye strictures of the esophagus. By dilatation with bougie through the gastrostomy the esophagus was rendered normally patent, thus affording entrance into the stomach both through the fistula and through the esophagus. Specimens obtained through the fistula showed consistently much more free and total acid and a higher CH than those obtained by stomach tube through the esophagus. These findings are best explained as the results of the increase of mucin and saliva in the gastric contents incident to the gagging and retching caused by the passage of the stomach tube.

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INDEX.

A

ABDOMINAL fat, subcutaneous, massive excision of, 601
 pain due to epigastric hernia, 748
 Torsion of omentum, 451
 Acoustic nerve, fibroma of, 772
 Acromegaly, hypophysis cerebri in, microscopic structure of, 153
 Actinotherapy in genital tuberculosis, 615
 Adenoma of breast, simple lactating, 731
 Adenomatous goiter, origin of, 622
 Adenomyoma of stomach, 466
 Adson, Alfred W., calorimetric studies of the extremities following lumbar sympathetic ramisection and gangliectomy, 232
 Agglutination, group, studies in, 776
 Allergic irritability, 924
 Alpers, Bernard J., nonfatal carbon monoxid poisoning, 390
 Amebic dysentery differentiated from idiopathic ulcerative colitis, 43
 Anders, James M., adiposity and other etiological factors in diabetes mellitus, 313
 Anemia, acute hemolytic, probably of infectious origin, 500
 in a newborn infant, 609
 pernicious, sprue and, 134
 splenic, 137
 Anemias of pregnancy and puerperium, 371
 Angina pectoris, neurological mechanism of, surgical therapy and, 864
 Anorectal surgery, problems of, 604
 Antigens and antibodies, union of heat produced by, 775
 Aorta, syphilis of, 905
 relation of morphology to prognosis of, 856
 Appelbaum, Emanuel, study of 450 cases of epidemic encephalitis, 708
 Appendicitis, acute, etiology of, 622 in aged, 907
 Armstrong, Eugene L., clinical and operative studies of opsonic index, 519
 Arteriovenous communications, abnormal, acquired and congenital, 761

Atkinson, Dorothy W., nontuberculous pulmonary fibrosis, 693

B

BACILLARY dysentery, vaccination by mouth against, 309
 Bacillus tetani, isolation, morphology, and cultural reactions of, 464
 Backache, diagnosis and treatment of, symposium on, 908
 Bacteria, relation of vegetative activity of, to pathogenicity, 312
 Bacterial factors in pyorrhea alveolaris, 923
 Bacteriologic study of nasopharynx in patients treated with chlorin inhalations, 300
 Bacteriophage with respect to complement-fixation tests, 464
 Baldwin, J. F., blood transfusion, dangers and value of, 118
 Bank, J., value of neutral red as test for gastric secretory function, 405
 Barrow, John V., clinical and operative studies of opsonic index, 519
 Bass, Murray H., eosinophilia with splenomegaly in a child, 416
 Bennett, A. E., atypical tabes dorsalis (forme fruste): surgical errors in, with leading points in diagnosis, 538
 Blood of morphin and heroin addicts, absence of transferable immunizing substances in, 155
 neutrophils in, prognostic value of differentiating immature, 600
 serum of pregnant women, Wassermann test in, 143
 transfusion, dangers and value of, 118
 phenomena concerned with reactions following, 913
 Blood-pressure determinations in major surgery, 909
 Blood-sedimentation test, 298
 Blood-stream infection through tonsils, 621
 Boas, Ernst P., mitral stenosis after fifth decade of life, 529
 Bockus, H. L., value of neutral red as test for gastric secretory function, 405

- Body weight in relation to health and disease, 564
- Bone and joint lesions of known syphilitic origin, analysis of, 919
- Bothe, Albert E., simple lactating adenoma of breast, 731
- Brain hemorrhage, extensive, 770
tumors, psychic manifestations in, 769
- Breast, adenoma of, simple lactating, 731
cancer of, surgical treatment of, 603
feeding, universalizing of, in a community, 765
- Breidigain, F. T., tropical sprue in a child, 364
- Bright's disease, clinical classification of, 447
- Brill's disease in Lower Rio Grande Valley, 155
- Bronchopneumonia in children, vaccine and serum treatment in, 612
- Brown, George E., calorimetric studies of the extremities following lumbar sympathetic ramisection and ganglionection, 232
tintometer for analysis of color of skin, 341
- Browne, John C., clinical value of recent tests for liver function, 510
- Buchbinder, William Charles, carcinoma of esophagus with reference to site, 496
- Burns, treatment of, tannic acid in, 760

C

- CANCER of breast, surgical treatment of, 603
of cervix, inoperable, irradiation of, 461
cutaneous, roentgen-ray treatment of, 150
infection, 290
of large bowel, early diagnosis of, 291
problem, 139, 768
production of, experimental, innervation a factor in, 467
by radium and Roentgen rays, in vitro cultivation of tissues and, 465
researches in, 778
soot, 465
of uterus, final results of treatment of, at Radiumhemmet, Stockholm, 302
radiotherapy in, 459
roentgenotherapy of, 616
use of radium in, 296
of vagina, 916
- Carbohydrate tolerance in myxedema, 907

- Carbon monoxide poisoning, bed sores in diagnosis of, 98
nonfatal, 390
- Carcinoma of esophagus, site and, 496
of lung, primary, 102
mammary, deep Roentgen-ray therapy of, 909
of rectum, pregnancy and, 451
- Cardiac fibrillation, cure of, 606
defects in children, congenital, 294
- Cecum, tuberculoma of, 139
- Cerebral hemisphere, tumors of, diagnosis and treatment of, 324
- Cerebrospinal fluid as index of otorhinogenic intracranial complications, 917
in infants and young children, 82
in syphilitic children, 455
- Cervix, cancer of, inoperable, irradiation of, 461
- Chlorine gas as a treatment for respiratory diseases, 299
in treatment of colds, value of, 301
- Cisterna magna, puncture of, 448
- Clostridium botulinum, pathogenicity of, 623
- Cod liver oil, radiations of, 140
- Colon, polyposis of, 759
- Congenital cardiac defects in children, 294
hypertrophic pyloric stenosis, 455
- Coramin, therapeutic value of, 911
- Criep, Leo H., generalized tuberculous adenitis, 822
- Crohn, Burrill B., sigmoidoscopic picture of chronic ulcerative colitis, 220
- Crowell, C., spontaneous rupture of heart, 828
- Cystic inflammation of vesical neck and prostatic urethra, 760

D

- DELINQUENTS and delinquency, review of some studies of, 769
- Dementia precox, aseptic meningitis in treatment of, 771
- Denis, W., study of effect produced on enzyme concentration of duodenum by oral administration of commercial pancreatic preparations, 727
- Dexter, Richard, observations on diagnosis of subphrenic abscess, 810
- Diabetes mellitus, adiposity and, 313
- Diabetic coma, relation of infection to, 289
- Diaphragmatic hernia, nontraumatic symptoms of, 290
- Diphtheria carriers, epidemiological importance of, 778
heart in, 295
of skin, 454
- Dislocations of elbow, 451

- Draper, George, studies in human constitution, 803
 Drug addiction, relation of intelligence to etiology of, 770
 Dublin, Louis I., physical defects as revealed by periodic health examinations, 576
 du Bray, Ernest S., body weight in relation to health and disease, 564
 Dunham, Royal W., effect of spleen extract and bone marrow in blood picture of pulmonary tuberculosis, 394
 Duodenal diverticulosis, 53

E

- Ectopic Muellierianoma, 298
 Eczema, focal infections in etiology of, 723
 - intravenous bromid therapy in, 613
 Eisen, David, malignant tumors of thyroid, 61
 Elbow, fractures and dislocations of, 451
 Electrokinetic behavior of mammalian serous membranes, 924
 Elsberg, Charles A., problems in the diagnosis and treatment of infiltrating tumors of cerebral hemispheres, 324
 Emery, E. S., Jr., effect of roentgenotherapy on human heart, 884
 Encephalitis, epidemic, 771
 study of 450 cases of, 708
 Encephalitogenic virus, exotic strain of, 151
 herpetic strains of, 151
 Endemic goiter problem, some aspects of, 138
 Endocervicitis, cautery treatment of, 458
 Endocrine therapy in gonad failure in male, 449
 Eosinophilia with splenomegaly in a child, 416
 Epidemic encephalitis in children, acute, difficulties in diagnosis of, 293
 Epididymis, gonorrhea of, 604
 Epilepsy, ketogenic diet for, 758
 in, 454
 luminal in treatment of, 607
 Epithelioma of vulva, 916
 Erythema of legs in young women due to thin stockings, 613
 Erythematous lupus, etiologic factors in, 614
 Esophagus, carcinoma of, site and, 496

F

- FARLEY, David L., purpura hemorrhagica (thrombocytopenic purpura) with report of case of splenectomy, 10

- Feldman, Maurice, report of an interesting type of diaphragmatic hernia of cardia of stomach through the esophageal orifice, 263
 Femur, fracture of single condyle of, treatment of, 138
 Fibroma of acoustic nerve, 772
 Fibromas of nasopharynx, treatment of, 918
 Filariasis, vascular, treatment of, 608
 Fisk, Eugene Lyman, physical defects as revealed by periodic health examinations, 576
 Fractures of elbow, 451
 reduction of, no-foreign body and tight-fitting window-cast in technic of, 450
 Friedenwald, Julius, report of an interesting type of diaphragmatic hernia of cardia of stomach through the esophageal orifice, 263
 Fries, Margaret E., glucose tolerance tests in children, 547
 Further indirect evidence that anaerobes tend to produce peroxid in presence of oxygen, 777
 Fusiform bacilli and spirochetes, studies on, 774

G

- GALL-BLADDER disease, roentgenologic diagnosis of, tetrabromphenolphthalein sodium salt in, 149
 Gastric analyses in infants, 610
 juice in children with gastrostomies, studies of, colorimetric and electrometric determination of hydrogen-ion concentration, 927
 secretions and motility in mental patients, 921
 secretory function, neutral red and, 405
 ulcer and gastric carcinoma, 605
 Gastrointestinal tract, chronic infection of, its roentgen-ray manifestations, 920
 Germicidal properties of soap, 780
 Giardiasis, 348
 Giffin, Herbert Z., review of 28 cases of purpura hemorrhagic in which splenectomy was performed, 186
 Glomerular capillary pressure in frog, estimation of, 925
 function, nature and mode of regulation of, 781
 Glucose tolerance tests in children, 547
 Glycogen and lipoids, combined microscopic demonstration of, 306
 Goiter, adenomatous, origin of, 622
 simple, prevention of, 1
 use of iodine in, 909
 Gonorrhea of epididymis, 604
 Gordon, Burgess, effect of roentgenotherapy on human heart, 884

Gordon, Burgess, value of venesection in treatment of decompensated heart, 671
 Graham, R. H., pyelitis in newly-born infants, 401
 Gray, Irving, left shoulder pain of phrenic origin, a reflex symptom in chronic appendicitis, 894

H

HARD-OF-HEARING, report of committee of section on Laryngology, Otology and Rhinology on, 619
 Harrah, James A., rectal ether analgesia in childbirth, 256
 Hathaway, J. C., prevention of simple goiter, 1
 Heart, decompensated, venesection in treatment of, 671
 disorders, quinidin sulphate in, 601
 in diphtheria, 295
 effect of roentgenotherapy on, 884
 rupture of, spontaneous, 828
 syphilis of, 905
 Hematuria, is there an essential? 449
 Hemolytic streptococcus, allergic reactions to, 776
 icterus, microcytosis in, 678
 Hepatic abscess, amebic type, radiographic findings in, 148
 function, surgical significance of, 137
 Hernia, diaphragmatic, nontraumatic, symptoms of, 290
 Hinton, J. William, abdominal pain due to epigastric hernia, 748
 Hirsch, Edwin F., differentiation of amebic dysentery from so-called idiopathic ulcerative colitis, 43
 Hodges, F. Churchill, three cases of tularemia, one resembling sporotrichosis, 57
 Hoffmann, Albert, experimental gastric and duodenal inflammation and ulcer, 212
 Holloway, Jackson K., review of twenty-eight cases of purpura hemorrhagica in which splenectomy was performed, 186
 "Hormone" medium, 305
 Hunter, John I., relationship of sympathetic innervation to tone of skeletal muscle, 469
 Humidity control in residences, 779
 Hypophysis cerebri in acromegaly, microscopic structure of, 153
 pathology of, 152

I

ILLNESS in a general population group, incidence of, 155, 309

Industrial dust problem, studies on, 156
 Infant feeding, supervision of dairy herd to prevent anaphylactic symptoms in, 453
 mortality, interracial variation in, 779
 Insulin in treatment of malnourished infant, 609
 Intestinal putrefaction, quantitative determination of, 888
 Intracranial injuries with or without fracture, management of, 605

J

JACKSON, Arnold S., iodine hyperthyroidism, 271
 Henry W., study of 450 cases of epidemic encephalitis, 708
 Jameson, H. Leon, adiposity and other etiological factors in diabetes mellitus, 313
 Jaundice, an expression of physiological wastage of corpuscles, 134
 Johnson, Gertrude, tropical sprue in a child, 364
 Johnson, William O., 100 consecutive cholecystectomies, 181
 Joint infections, acute pathogenic, treatment of, 452

K

KAHN and Wassermann test, comparison of, 906
 Keloid nonpostcircumcised, 425
 Ketogenic diet for epilepsy, 758
 Kidney, movable, 297, 452
 Kohn, Jerome L., glucose tolerance tests in children, 547
 Kopf, Edwin W., physical defects as revealed by periodic health examinations, 576
 Kottman reaction in thyroid dysfunction, 75
 Kramer, David W., Kottman reaction in thyroid dysfunction, 75
 Krumbhaar, E. B., spontaneous rupture of heart, 828

L

LABYRINTH of inner ear *in situ*, new method of demonstrating, 301
 Landon, John, conditions simulating acute lymphatic leukemia, 37
 Larrabee, Ralph C., severe anemias of pregnancy and puerperium, 371
 Leche, Stella, study of effect produced on enzyme concentration of duodenum by oral administration of commercial pancreatic preparations, 727

- Lederer, Max, acute hemolytic anemia probably of infectious origin, 500
 Leptospirosis icterohemorrhagica, 332
 Lipiodol in neurosurgery, 874
 Lipschutz, Emanuel W., duodenal diverticulosis with report of a case seen roentgenologically, 53
 Liver, diseases of, biliary aspects of, 625
 tests of hepatic function in, 758
 function, clinical value of recent tests of, 510
 necrosis of, in an infant, 463
 Luetin test, nonspecificity of, 614
 Lung abscess following tonsillectomy, 619
 carcinoma of, primary, 102
 lesions, chronic, differential diagnosis of, 302
 Lungs, vital capacity of, clinical medicine and, 601.
 Lymphatic leukemia, acute, conditions simulating, 37
 Lymphogranuloma, benign, nature of, 144
 Lyon, B. B. Vincent, giardiasis; its frequency, treatment and certain clinical factors, 348
- M**
- McCAFFERTY, Lawrence K., Wassermann-fast syphilitics treated with bismuth, 22
 MacGregor, J. Arnot, Wassermann-fast syphilitics treated with bismuth, 22
 MacLachlan, W. W. G., relation of morphology to the prognosis of aortic syphilis, 856
 Maclaire, A. S., lipiodol in neurosurgery, 874
 McLean, Stafford, cerebrospinal fluid in infants and young children, 82
 Major, Ralph H., possible relationship between guanidin and high blood-pressure, 228
 Malaria, eight weeks' quinin treatment of, 308
 quinin salts in, indications for intravenous injection of, 910
 Malarial parasites, "thick-film" examination for, 134
 Mammalian serous membranes, electrokinetic behavior of, 924
 Maxillary sinus disease, comparative value of transillumination and roentgenography in diagnosis of, 620
 Mayers, Lawrence H., differentiation of amebic dysentery from so-called idiopathic ulcerative colitis, 43
 Menninger, Karl A., Wassermann reaction in blood and spinal fluid of parietic neurosyphilis, 27
 Menninger, William C., Wassermann reaction in blood and spinal fluid of parietic neurosyphilis, 27
 Mental examination of college men, 770
 testing, developments in field of, 311
 Metabolism, energy, of premature and undersized infants, 913
 Meyer, Willy, some notes on cancer, 481
 Miller, T. Grier, consideration of the clinical value of ephedrin, 157
 Mitral stenosis after fifth decade of life, 529
 Monilia psilosis relation of sprue and pernicious anemia to, 134
 Morphin poisoning, experimental, 136
 Moses, Henry Monroe, primary carcinoma of lung, 102
 Movable kidney, 297, 452
 Mumps of pancreas, 293
 Myeloid myelomata, 920
 Myxedema, carbohydrate tolerance in, 907
- N**
- NARR, Fred C., generalized tuberculous adenitis, 822
 Nasal cavity of dogs, abnormal development of, due to interruption of respiratory current, 773
 Nasopharynx, fibromas of, treatment of, 918
 Nathanson, M. H., disease of the coronary arteries, 240
 Neal, Josephine B., study of 450 cases of epidemic encephalitis, 708
 Necrosis of liver in an infant, 463
 Nephritis, acute, in children, 143
 experimental oxalate, renal circulation rate in, 777
 primary vascular, 757
 uremia and, 905
 Neurosurgery, lipiodol in, 874
 Newborn infant, anemia in, 609
 Nichols, John Benjamin, pharmacological and therapeutic properties of sulphocyanates, 735
 Novello, N. Jean, quantitative determination of intestinal putrefaction, 888
- O**
- OLDS, William H., clinical and operative studies of opsonic index, 519
 Omentum, abdominal torsion of, 451
 Opsonic index, clinical and operative studies of, 519
 Organic processes, experimental, negative histologic findings in, 770
 Oto-rhino-laryngology, Fahræus blood sedimentation test in, 463
 Ovarian dermoids, 617

P

- PANCREAS, mumps of, 293
 Paratyphoid-enteritidis group, differentiation of, 304
 Parenchymal rales in pulmonary tuberculosis, 599
 Paresis, general, malarial inoculation treatment for, 303
 Paretic neurosyphilis, Wassermann reaction in blood and spinal fluid of, 27
 Parotitis, postoperative, 907
 Patella, congenital anomaly of, 149
 Pelvic inflammatory disease, 915
 Penfield, Wilder, neurological mechanism of angina pectoris and its relation to surgical therapy, 864
 Peptic ulcer, gastric motor activity and, 136
 merits of various treatments of, 292
 Periarterial sympathectomy, 762
 Perinephritic abscess in children, 761
 Peritonitis, static, in malnourished infants, 764
 Perla, David, mitral stenosis after fifth decade of life, 529
 Pernicious anemia, analysis of fecal flora in 33 cases of, 923
 Phagocytosis of erythrocytes in bone marrow with special reference to pernicious anemia, 305
 Piersol, George Morris, value of neutral red as test for gastric secretory function, 405
 Plague: past, present and future, 600
 Pneumococci during growth *in vitro*, variation in specificity and virulence of, 307
 Pneumonia associated with bacillus abortus in fetuses and newborn calves, 624
 in children, 294
 experimental, in mice following inhalation of *Streptococcus hemolyticus* and Friedländer's bacillus, 307
 following nasopharyngeal injections of oil, studies on, 773
 Pneumothorax, diagnostic, 148
 Poisoning, morphin, experimental, 136
 Poliomyelitis, anterior, residual paralysis and deformity of, 760
 Polyposis of colon, 759
 Pomeroy, Lawrence A., acute typhoid cholecystitis forty-one years after original infection, 881
 Pottenger, F. M., increased permeability of vessel walls as cause of pulmonary hemorrhage, 420
 Pregnancy, anemias of, 371
 Preston, Majorie, clinical value of recent tests for liver function, 510
 Prostactic urethra, cystic inflammation of, 760

- Psoriasis, salicylate of soda in treatment of, 144
 Psychiatry, relation of social work to, 922
 Puerperium, anemias of, 371
 Pulmonary fibrosis, nontuberculous, 693
 hemorrhage, increased permeability of vessel walls and, 420
 Purpura hemorrhagica, 10
 treatment of syphilis and, 614
 Pyelitis in newly-born infants, 401
 Pyloric stenosis, congenital hypertrophic, 455
 hypertrophic, surgery of, 603
 in infants, 912
 Pyorrhea alveolaris, bacteria factors in, 923

R

- RABINOWITZ, Meyer A., early bed sores as diagnostic sign of carbon monoxid poisoning, 98
 Radiotherapy in malignant disease, 291
 Rectum, carcinoma of, pregnancy and, 451
 Red blood cells, human, incidence of two types of Group II, 466
 Renal neoplasms, clinical and surgical aspects of, 96
 periarteritis nodosa, 757
 Reviews—
 Alexander, Surgery of Pulmonary Tuberculosis, 900
 Allbutt, Arteriosclerosis, 903
 Appleton, Bacterial Infection, 595
 Bachem, Neuere Arzneimittel, 443
 Ballenger, Diseases of the Nose, Throat and Ear, 901
 Bell, Feeding, Diet and General Care of Children, 130
 Boyd, Preventive Medicine, 902
 Bram, Goiter: Neurosurgical Types and Treatment, 597
 Brown, Physiological Principles in Treatment, 128
 Collected Papers of Mayo Clinic and Mayo Foundation, 1924, 756
 Collins, Pathology and Bacteriology of Eye, 129
 Coombs, Rheumatic Heart Disease, 442
 Copher, Methods in Surgery, 904
 Crummer, Clinical Features of Heart Disease, 443
 Cushny, Action and Uses in Medicine, of Digitalis, 442
 Da Costa, Modern Surgery, 287
 de Martell and Antoine, Pseudo-appendicitis, 130
 Dorland, Medical Dictionary, 596
 Elsberg, Tumors of Spinal Cord, 128
 Fishbein, The Medical Follies, 904

Reviews—

- Fisher, Statistical Methods for Research Workers, 446
 Flint, Manual of Physical Diagnosis, 127
 Friedenwald, Diet in Health and Disease, 129
 Ghosh, *Materia Medica*, 130
 Treatise on Hygiene and Public Health, 130
 Materia Medica and Therapeutics, 130
 Gray, A Synopsis of Gynecology, 445
 Gulland and Goodall, the Blood, 754
 Hamilton, Industrial Poisons in the United States, 595
 Hays, Diseases of the Ear, Nose and Throat, 445
 Hutchison, Lectures on Dyspepsia, 754
 Hutchison and Sherran, An Index of Treatment, 902
 International Medical Annual, 597
 Quevli, Enzyme Intelligence and Whence and Whither, 755
 Jackson, Effects of Inanition and Malnutrition on Growth and Structure, 132
 Jellett, Practice of Gynecology, 284
 Jordan, General Bacteriology, 598
 Kanavel, Infections of Hand, 127
 Kolmer and Boerner, Laboratory Diagnostic Methods, 284
 Loeb, Proteins and Theory of Colloidal Behavior, 753
 Lord, Diseases of Bronchi, Lungs and Pleura, 900
 Low, Anaphylaxis and Sensitization, 753
 Lull, Compend of Obstetrics, 756
 Manson-Bahr, Tropical Diseases, 285
 Marshall, An Introduction to Sexual Physiology, 444
 Medical and Surgical Report of Roosevelt Hospital, 598
 Michaelis, Effects of Ions in Colloidal Systems, 286
 Mortality Statistics (1922), 596
 Nutt, Diseases and Deformities of the Foot, 285
 of Digitalis and Its Allies, 442
 Pappenheim and Caffrey, Lumbar Puncture, 288
 Pearce and Macleod, Fundamentals of Human Physiology, 131
 Pratt and Bushnell, Physical Diagnosis of Diseases of the Chest, 286
 Proceedings of the International Conference on Health Problems in Tropical America, 287

Reviews—

- Proceedings of the Third International Congress of the History of Medicine at London, 1922, 755
 Ringer, Clinical Medicine for Nurses, 131
 Schamberg, Compend of Diseases of Skin, 756
 Stocks, Hereditary Disorders of Bone Development, 445
 Turner, Personal and Community Health, 902
 Vaquez, Medicaments et Medications Cardiaques, 444
 von Monakow, The Emotions, Morality and the Brain, 129
 Walker, Diseases of Male Organs of Generation, 132
 Webb and Ryder, Recovery Record for Use in Tuberculosis, 288
 Wright, Conquest of Cancer, 596
 Rheumatic fever, 631
 infections in childhood, 142
 Richards, A. N., nature and mode of regulation of glomerular function, 781
 Rickets, control of, 763
 Riecker, Herman H., clinical study of quinidin therapy, 205
 Rickettsia, their relationship to disease, 310
 Roentgenotherapy of uterine cancer, 616
 Roentgen-ray manifestations of chronic infection of gastrointestinal tract, 919
 Rosenberg, Herman, sigmoidoscopic picture of chronic ulcerative colitis, 220
 Rous, Peyton, biliary aspects of liver disease, 625
 Rowntree, Leonard G., tintometer for analysis of color of skin, 341

S

- SAILER, Joseph, leptospirosis ictero-hemorrhagica, 332
 Salvarsan infiltration, method for immediate treatment of, 608
 Scarlet fever, etiology, prevention by immunization and antitoxic treatment of, 912
 results of Dick test before and after immunization with hemolytic streptococcus, 154
 skin test for susceptibility to, 141
 Schoenheit, Edward W., magnesium and calcium content of blood and blood plasma in tuberculous patients, 689

- Segall, Harold N., clinical observations on the value of calcium chlorid as a diuretic and on its influence on the circulatory mechanism, 647
- Sensitization to adhesive plaster, 614
- Shattuck, Howard F., clinical value of recent tests for liver function, 510
- Shen, James K., acute typhoid cholecystitis forty-one years after original infection, 881
- Sherwin, C. P., quantitative determination of intestinal putrefaction, 888
- Silverman, Daniel N., study of effect produced on enzyme concentration of duodenum by oral administration of commercial pancreatic preparations, 727
- Sinus disease in children, recognition of, 621
- Skeletal traction, 603
- Skin, diphtheria of, 454
disinfectant, preoperative, 762
sensitization to sunlight, treatment of by peptone injections, 613
test for susceptibility to scarlet fever, 241
- Soap, germicidal properties of, 780
- Soot cancer, experimental, 465
- Sphenopalatine ganglion, study of, 618
- Spinal cord, subacute combined degeneration of, 135
tumors of, use of lipiodol in, 771
- Sprue, pernicious anemia and, 134
tropical, in a child, 364
- Splenic anemia, 137
- Staphylococci from liver, gall-bladder and intestine of normal dogs, 775
- Stomach, adenomyoma of, 466
syphilis of, 138
- Stricture of, ureter, 460
- Strychnin, use of, for disturbances of balance, in subjective sounds in ears and in defective hearing, 618
- Subphrenic abscess, 431
diagnosis of, 810
- Sulphocyanates, pharmacologic and therapeutic properties of, 735
- Swalm, William A., giardiasis: its frequency, treatment, and certain clinical factors, 348
- Swift, Homer F., rheumatic fever, 631
- Syphilis of aorta, 905
relation of morphology to prognosis of, 856
experimental in rabbit, potassium iodid and, 615
of heart, 905
of stomach, 138
treatment of, purpura hemorrhagica and, 614
of urinary bladder, 450
wound healing in, 909
- Syphilitic children, cerebrospinal fluid in, 455
- Syphilitics, Wassermann-fast, bismuth and, 22

T

- TABES dorsalis, atypical, 538
- Temperatures, high environmental, effects of on the organism, 467
- Tetanus from vaccination dressings, 154
- Tetany a cause of convulsions in very young infants, 295
- Thymus glands, study of, 140
- Thyroid, dysfunction, Kottman reaction in, 75
tumors of, malignant, 61
- Thrombocytopenic purpura, 10
- Tongue, tuberculosis of, 762
- Tonsillectomy, lung abscess following, 619
microscopic study of excised tonsil in relation to, 462
- Tonsils, blood-stream infection through, 621
- Treponema pertenu in rabbit, characteristics of infections produced by, 133
- Trichomonas intestinalis, pathogenicity of, 758
- Tubal gestation, correlation of uterine and tubal changes in, 147
- Tubal pregnancy, ruptured, autotransfusion in, 767
- Tuberculoma of cecum, 139
- Tuberculosis in children, 610
diagnosis of, 611, 912
genital, actinotherapy in, 615
pulmonary, bone marrow and, 394
parenchymal rales in, 599
spleen extract and, 394
of tongue, 762
- Tuberculous adenitis, generalized, 822
meningitis in children, 456
- Tuft, Louis, subphrenic abscess, 431
- Tularemia, case resembling sporotrichosis, 57
- Tumors of thyroid, malignant, 61
of ureter, primary, 306
of uterus, benign, irradiation of, 457
- Typhus, mild, in Lower Rio Grande Valley, 155

U

- UREMIA, nephritis and, 905
- Ureter, stricture of, 460
tumors of primary, 306
- Ureteral calculi, treatment of, basis for comparing results in, 761
calculus, nonoperative treatment of, 145
stricture and urinary calculus, roentgenoscopic evidence of association of, 602

Ureters, spastic obstruction to, 602
 Urethral implantation, bilateral, 766
 Urinary bladder, syphilis of, 450
 Urine, residual, in women, 459
 Urotropin, action of intravenous injection of solution of 40 per cent of, 608, 910
 Uterine hemorrhage, radium and roentgen radiation in treatment of, 150
 Uterus, cancer of, final results of treatment of, at Radiumhemmet, Stockholm, 302
 radiotherapy in, 459
 roentgenotherapy of, 616
 use of radium in, 296
 tumors of, benign, irradiation of, 457
 coincidence of, 914

V

VAGINA, cancer of, 916
 Vascular nevi, roentgenotherapy of, 148
 Vesical neck, cystic inflammation of, 760

Visher, John W., focal infections in etiology of eczema, 723
 von Hofe, Frederick H., cerebrospinal fluid in infants and young children, 82
 Vulva, epithelioma of, 716

W

WALDBOTT, George L., observations on nonpostcicatricial keloid, 425
 Wassermann test on blood serum of pregnant women, 143
 sulpharsphenamin and, 615
 Weil's disease, 332
 Whitchee, B. R., microcytosis in hemolytic icterus, 678
 White, Paul D., clinical observations on the value of calcium chlorid and on its influence on the circulatory mechanism, 647
 Whooping cough, does roentgen ray modify course of, 764
 Wolf, William, quantitative determination of intestinal putrefaction, 888

